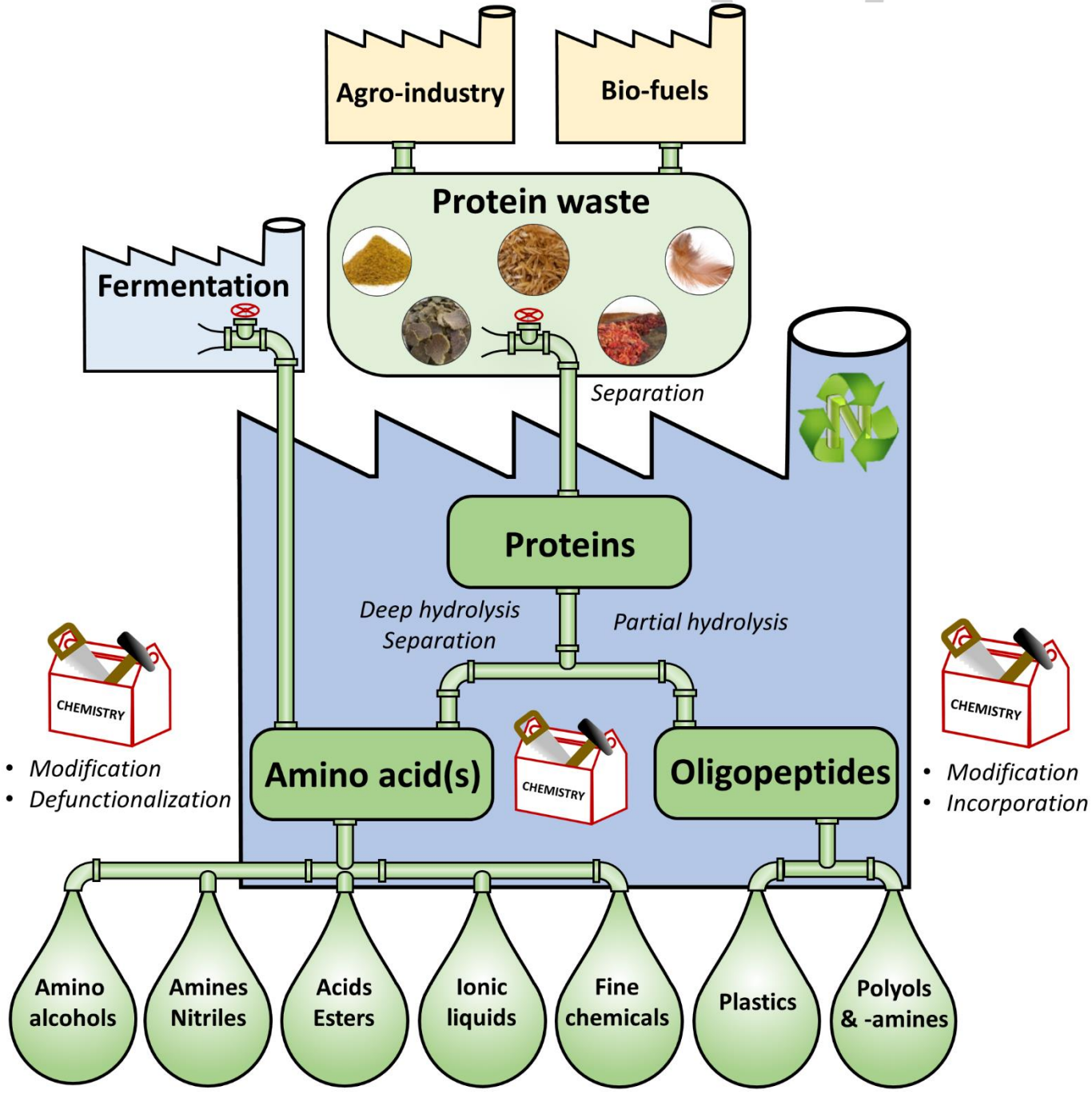
Protein-rich biomass waste as a resource for future bio-refineries: state of the art, challenges and opportunities

Free De Schouwer,[§[a]] Laurens Claes,[§[a]] Annelies Vandekerkhove,[[a]] Jasper Verduyckt and Dirk E. De Vos*[[a]]

[§] These authors contributed equally.



Abstract: Protein-rich biomass provides a valuable feedstock for the chemical industry. In this review article we will cover every process step in the value chain from protein waste to chemicals. The first part deals with the physicochemical extraction of proteins out of biomass, the hydrolytic degradation to peptides and amino acids, and the separation of amino acid mixtures. The second part provides an overview of physical and (bio)chemical technologies for the production of polymers, commodity chemicals, pharmaceuticals and other fine chemicals. This can be achieved by incorporation of oligopeptides into polymers, or by modification and defunctionalization of amino acids, a.o. reduction to amino alcohols, decarboxylation to amines, (cyclic) amides and nitriles, deamination to (di)carboxylic acids and synthesis of fine chemicals and ionic liquids. Bio- and chemocatalytic approaches are compared in terms of scope, efficiency and sustainability.

1 Introduction

Nowadays the global economy relies on fossil resources for the production of fuels and chemicals. However, fluctuating oil prices, geopolitical factors and concerns about environmental issues associated with the emission of greenhouse gases such as CO_2, CH_4, N_2O *etc*. strongly boost the transition towards a bio-based chemical industry.[1–4] For instance, the European Union has the ambition to reduce greenhouse gas emissions by 20%, and to let energy production depend for at least 20% on renewable resources by 2020; moreover, according to a 2030 framework for climate and energy policies, these targets should be almost doubled by 2030.[5] To that end, non-edible biomass has been considered as an alternative, renewable feedstock for the production of fuels and chemicals. In an integrated bio-refinery, fuels cover the major volume but are of relatively low value, whereas the production of high-value bulk and fine chemicals provides the main stimulus to reach the economic goals.[6,7]

Plant-based biomass consists of carbohydrates (in particular cellulose, hemicellulose and starch; *ca.* 75%) and lignin (*ca.* 20%), and the remaining fraction comprises triglycerides (a.o. fats and oils), proteins and terpenes; the exact composition differs among various feedstocks.[3,7] Many functionalized chemicals in the current product portfolio of the petrochemical industry have a backbone structure which can be retrieved from these biomass constituents. Consequently, the number of process steps and the amount of energy and reagents can be reduced when these chemicals would be produced from biomass rather than from oil or natural gas.[1,2,4,8] In the past decade research on biomass valorization has mainly focused on the (bio)chemical conversion of the C-, H- and O-containing fractions (*viz.* carbohydrates, lignin and triglycerides),[3,6,9–11] whereas the N-containing fraction (*viz.* proteins) has received only little attention so far.[12]

Amino acids have nowadays numerous applications in the production of food and beverages, animal feed, pharmaceuticals, cosmetics and agrochemicals. For example, lysine is an important nutritional additive in animal feed for pig breeding and poultry farming; monosodium glutamate (MSG) is a flavor enhancer in many food products, and aspartic acid and phenylalanine are the main building blocks of aspartame, which is a common sugar replacer in beverages.[13,14] Besides, proteins and amino acids have a huge potential for the production of N-containing chemicals in a bio-refinery, provided that there is no competition with food production. In that respect glutamic acid and aspartic acid have been proposed by the US Department of Energy as potential bio-based platform molecules for the chemical industry because they can be obtained by fermentation from carbohydrates. Although the development of cost-efficient large-scale production processes often remains a major challenge,[12] additional bulk quantities of amino acids can be retrieved from protein-rich biomass waste from the agro-industry and bio-fuel production. For example, in 2015 more than 40 million tons of dried distiller grains with solubles (DDGS) were available from bio-ethanol production in the United States.[15] Until now protein-rich waste streams are processed into animal feed, or combusted for energy recuperation in case of poor nutritional quality or toxicity. However, plant-based proteins contain a large fraction of non-essential amino acids, which are directly degraded and excreted by animals. In this way, nitrogen is released to the soil and the surface water as nitrate salts, and to the atmosphere as the greenhouse gas N_2O.[16,17] Consequently, converting protein waste to N-containing chemicals would result in a more efficient nitrogen cycle and a strong decrease in energy and environmental impact.[16] Such a valorization scheme roughly consists of four stages: (i) extraction of proteins from biomass; (ii) hydrolysis of proteins; (iii) fractionation of aqueous amino acid mixtures and (iv) (bio)chemical conversion of amino acids to valuable end products (Figure 1). In an ideal scenario the essential amino acids are used for animal feed formulation and only the non-essential ones are supplied as a raw material to the chemical industry.[18] The high degree of functionality and the presence of at least one chiral center in most amino acids allows to synthesize a wide range of bulk and fine chemicals, *e.g.* amines, nitriles, (cyclic) amides, (di)carboxylic acids, (chiral) amino alcohols, ionic liquids *etc*. Amino acids, (oligo)peptides and peptide-derived polyols and polyamines are also interesting building blocks for polymer synthesis.

The aim of this review is to discuss the current trends, challenges and opportunities in the valorization of protein-rich biomass to chemicals. In an initial section the availability of proteins and amino acids as well as the pre-treatment of proteins will be considered. Next, state-of-the-art and emerging (bio)chemical conversion technologies of amino acids and oligopeptides will be evaluated in terms of scope, current process issues, economical relevance and product applicability.

[a] Dr. F. De Schouwer, Dr. L. Claes, A. Vandekerkhove, Dr. J. Verduyckt, Prof. D. E. De Vos
Centre for Surface Chemistry and Catalysis
Department of Microbial and Molecular Systems
KU Leuven
Celestijnenlaan 200F, post box 2461, 3001 Heverlee, Belgium
E-mail: dirk.devos@kuleuven.be

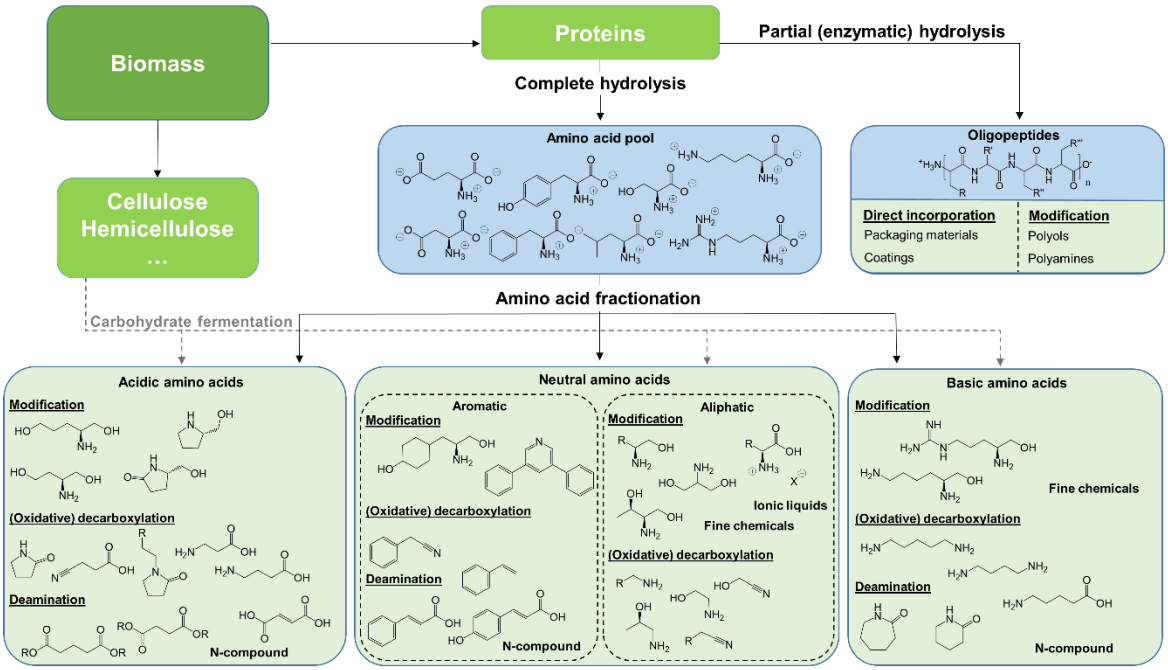


Figure 1. Valorization of protein-rich biomass to a range of bulk and fine chemicals by modification and defunctionalization of oligopeptides and amino acids.

Biographical Sketch.

((Author Portrait))

Biographical Sketch.

((Author Portrait))

2 Availability and pre-treatment of raw materials

2.1 Amino acid production

The world annual production of amino acids amounted to about 6.5 million tons in 2014 and the market volume is still expected to grow at a rate of about 6-8% per year.[19] Nowadays, glutamic acid (as monosodium salt), lysine (as hydrochloride salt), methionine and threonine cover more than 95% of the total market volume; they are mainly involved in food and animal feed applications (Table 1). However, with a growing world population, the tendency to eat more meat and the development of a bio-based society,[20] the demand for cheaper amino acids will provide new challenges and opportunities for chemical companies and key amino acid manufacturers such as Adisseo, Ajinomoto Co., Cargill Inc., Archer Daniels Midland (ADM), Aventis SA, ChemChina, Evonik Industries AG, Tokyo Chemical Industry Co., Arkema, CJ CheilJedang Co., Kyowa Hakko Bio Co. *etc*.[19,21,22] The methods applied in the industrial production of amino acids can be divided into four categories: microbial aerobic fermentation, enzymatic catalysis, chemical synthesis and extraction from natural resources.[13,23,24] Selection of the most appropriate method for each amino acid depends on the process economics, market size, availability of raw materials and environmental regulations.[13]

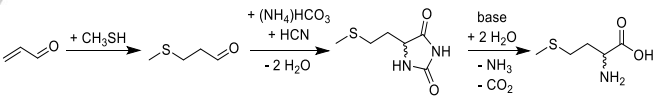
Table 1. Production and applications of the most important amino acids.

Amino acid	Production method	Application	Market volume (Mton)	Price (€ ton^{-1})
Monosodium L-glutamate	Fermentation by *C. glutamicum*	Flavor enhancer in food	3	1,000
L-Lysine·hydrochloride	Fermentation by *C. glutamicum*	Feed nutrient	2.4	1,200
D,L-Methionine	Chemical synthesis	Feed nutrient	1	2,500
L-Threonine	Fermentation by *E. coli*	Food and feed nutrient	0.6	1,350

The majority of the L-amino acids are nowadays produced by fermentation.[13,14,21,25–27] In the 1950's, this method has been developed after the discovery of the soil bacterium *Corynebacterium glutamicum*, an overproducer of glutamic acid from carbohydrates.[28] Metabolic engineering and strain improvements of *C. glutamicum* allowed to reach very high productivities and enabled the industrial-scale production of monosodium glutamate and lysine·hydrochloride at low prices (Table 1). *Escherichia coli*, another well-developed microbial strain, is involved in the large-scale production of threonine and tryptophan. The fermentation generally proceeds in an aqueous medium containing essential nutrients such as sources of carbon, nitrogen, sulfur and phosphorus, vitamins and minerals.[13,14,25,29] Identifying a suitable carbon source is a major challenge, because it should not only serve as an energy source for the micro-organism, but also as a precursor for the structural skeleton of the amino acid metabolite. Typical examples are starch hydrolysates from corn, cassava or potato, and sugar cane and sugar beet molasses. However, to meet the increasing demand for cheap amino acids, the research focus has shifted to the design of recombinant *C. glutamicum* and *E. coli* strains that are able to grow directly on other renewable, non-edible and inexpensive carbon sources, *e.g.* lignocellulosic waste (*viz.* xylose and arabinose from hemicellulose, and cellobiose), whey (*viz.* lactose and galactose), silage (*viz.* glucose and lactic acid) or glycerol, a major side product from biodiesel production.[26,30–32]

Enzymatic catalysis is currently the most viable strategy for the production of aspartic acid, tryptophan, cysteine and alanine. For instance, aspartic acid is obtained by the addition of ammonia (NH_3) to fumarate, which is catalyzed by aspartate ammonia-lyase. Eventually, alanine can be produced by a consecutive decarboxylation of aspartic acid mediated by aspartate β-decarboxylase. The enzymatic production process benefits from very high product concentrations, high productivity, high product purity and ease of separation. However, the application of aspartic acid as a building block in the chemical industry is nowadays limited by the lack of a cost-efficient and bio-based production process for fumaric acid.[12,33] A direct fermentative production process for aspartic acid that is cost-competitive with the existing enzymatic route could be another attractive solution.[12]

The chemical synthesis of amino acids is typically based on the Bucherer-Bergs variant of the Strecker reaction, which proceeds *via* a hydantoin intermediate that is generated from an aldehyde, hydrogen cyanide (HCN) and an ammonium salt (Scheme 1).[34] However, this approach is far less attractive than fermentation or enzymatic catalysis, because an expensive optical resolution step is required to isolate the bio-active L-isomer from the amino acid racemate. This approach is therefore only involved in the production of achiral glycine and D,L-methionine since adults and animals are able to convert D-methionine to the L-isomer by transamination.[14] Although both amino acid enantiomers are tolerated by many (bio)chemical conversion technologies, state-of-the-art chemical synthesis methods are generally not cost-competitive with fermentative production processes. Nevertheless, the chemical synthesis of amino acids from plant-based biomass is gaining attention. Recently a two-step chemical process has been designed for the bio-based production of amino acids from α-hydroxy acids, which can be obtained from lignocellulose. Ruthenium nanoparticles supported on carbon nanotubes facilitate both the dehydrogenation of α-hydroxy acids and the subsequent reductive amination of α-keto acids in aqueous NH_3 at 220 °C under 10 bar H_2.[35] In this way, alanine was obtained in 62% yield from lactic acid, corresponding with 43% yield based on glucose, which is comparable with the outcome of a fermentation process.



Scheme 1. Chemical synthesis of D,L-methionine from acrolein, methyl mercaptan, hydrogen cyanide and ammonium bicarbonate, involving a hydantoin intermediate.

Extraction of amino acids from natural resources was the main production method before the advent of fermentation technologies. For instance, monosodium glutamate was extracted from wheat gluten and de-oiled soybean, but this process was largely superseded due to the unfavorable economics and sustainability.[21,36] Nevertheless, it is well conceivable that this approach can gain ground again to rely on a bio-based industry. In fact, protein-rich biomass waste is nowadays abundantly available from the agro-industry and the production of bio-fuels.[18] Except for wheat gluten, whey protein and gelatin, these waste streams show insufficient nutritional quality for food/feed applications and provide an excellent and relatively cheap source

Table 2. Protein contents and prices of various protein-rich biomass residuals.

Biomass stream	Protein content (%, dry weight basis)	Price (€ ton^{-1} biomass)	Estimated price (€ ton^{-1} protein)	Ref.
Dried distillers grains with solubles	20-40	100-150	400	[18,37–39]
Sugar beet vinasse	15-30	150-180	700	[18,38]
Castor bean meal	30-60	100-130	300	[40,41]
Soybean meal	45-55	300	600	[39]
Poultry feather meal	80-90	300	350	[18,38,42]

of peptides and amino acids: *e.g.* dried distillers grains with solubles (DDGS) from wheat, maize and sorghum; sugar beet and sugar cane vinasses from bio-ethanol production; press cakes from soybean, palm and rapeseed oil production; leaves of many crops;[18] poultry feather meal; proteins from coffee or tea production[8] *etc*. Feather meal, DDGS and many press cakes are typically processed into animal feed; vinasses are used as such as fertilizers on the field, and leaves are often just left on the field.[43] However, due to the inefficient uptake of nitrogen by animals and the soil, and due to the ecological issues associated with acidic vinasses, the (bio)chemical conversion of these waste streams to bio-based chemicals could give rise to more efficient and valuable applications.[18] Besides, an annual increase of 100 million tons of protein waste is expected when 25% of the transportation fuels would be substituted by bio-fuels in Europe by 2030;[44] hence the production of animal feed and chemicals can go hand in hand.[1] Even more attractive are waste streams which are not (directly) involved in any food/feed applications due to legislation issues, toxicity or microbial contamination: *e.g.* fish protein, blood meal and other slaughterhouse waste;[45] food waste,[46] as one third of all food produced for human consumption is now spilled or wasted; press cakes from castor oil[47] and rapeseed oil production[47,48] *etc*. They are often combusted for energy recuperation or require detoxification prior to use.

In general, the prices of protein-rich waste streams are mainly dependent on the application, the protein content and the nutritional value of the protein fraction (*viz.* the amino acid composition, in particular the fraction of essential amino acids). Obviously, expensive protein sources such as wheat gluten (1,200 € ton^{-1}) and whey protein (35% protein, 2,000 € ton^{-1}) have applications in the food industry and will therefore not be considered for any technical application. Non-edible proteins are far more interesting in that respect (Table 2). A clear example is DDGS with protein contents up to 40% and prices in the range of 100-150 € ton^{-1}. Scott and Sanders proposed a variety of petrochemical products with values between 1,400-3,000 € ton^{-1} which eventually can be obtained from amino acids, thereby highlighting the large price gap between the raw materials and potential end products.[2] Furthermore, it is obvious that the market price of waste streams associated with bio-fuel production will decrease with increasing production volumes in the future.[1]

The amino acid composition differs strongly among the raw materials (Table 3) and even from one harvest or one geographical location to another. Nevertheless, glutamic acid is generally the most abundant amino acid constituent in plant-based protein hydrolysates. For instance, in wheat DDGS and sugar beet vinasses the overall content of glutamic acid and glutamine can reach 34% and 55%, respectively. Also aspartic acid and asparagine can be present in substantial amounts, *e.g.* about 10% in castor bean meal and soybean meal. Therefore, the acidic amino acid fraction has often been suggested to have the highest potential for the production of chemicals.[18,49,50] Moreover, both glutamic acid and aspartic acid are non-essential amino acids, hence, they will not compete with feed applications. Besides, the essential amino acids (*viz.* phenylalanine, valine, leucine, isoleucine, lysine, threonine, tryptophan and methionine) constitute only 30-40% of the total protein content. Consequently, the separation of essential amino acids from non-essential ones would provide an interesting feedstock for a bio-based chemical industry, without decreasing the nutritional value of the residue for animal feed applications.

2.2 Amino acid production

When using protein-rich biomass as a raw material in a bio-refinery, proteins should be separated first from the other biomass constituents such as carbohydrates, lignin and triglycerides.[20] Although the separation can be achieved by extraction under both alkaline and acidic conditions, the former approach is generally preferred due to a better breakdown of cell wall components, fat saponification and a higher protein solubility. In contrast, under acidic conditions the pH is closer to the isoelectric point of proteins, hence, the relatively hydrophobic proteins will have less net charge resulting in a lower solubility. Nevertheless, alkaline extraction has also several drawbacks such as low cost-efficiency due to the overuse of chemicals, risk of amino acid racemization, degradation of some amino acids and salt waste formation. The extraction efficiency is also dependent on the properties of the raw materials, such as biomass cell wall rigidity, chemical composition of the cell,[48,51] protein storage location,[52] and protein structure. Therefore, traditional extraction methods are often insufficient for protein-rich biomass with a higher degree of complexity.

Table 3. Amino acid composition (in wt%) of various protein-rich biomass residuals, determined after hydrolysis under acidic conditions.

Amino acid	Wheat DDGS[18]	Sugar beet vinasse[18]	Cassava leaves[18]	Castor bean meal[53]	Soybean meal[18]	Poultry feather meal[42]
Glycine (Gly)	4.5	3.6	7.0	5.0	4.0	7.3
Alanine (Ala)	4.3	4.5	7.7	4.8	4.3	5.9
Valine (Val)	4.8	2.9	0.0	5.9	5.1	6.6
Leucine (Leu)	6.6	3.2	11.6	7.0	7.5	8.2
Isoleucine (Ile)	3.4	2.7	6.8	4.7	5.2	4.9
Serine (Ser)	4.5	3.2	6.2	6.0	4.9	10.7
Threonine (Thr)	3.4	1.9	0.0	3.9	3.8	4.2
Cysteine (Cys)	1.1	0.0	1.3	2.6	1.6	4.2
Methionine (Met)	1.6	4.2	2.9	1.9	1.4	5.6
Proline (Pro)	10.3	3.2	0.0	4.2	4.5	8.5
Phenylalanine (Phe)	4.7	1.5	7.2	4.5	4.9	4.8
Tyrosine (Tyr)	3.3	1.9	5.7	0.0	3.3	2.4
Tryptophan (Trp)	0.0	0.8	2.7	/ [a]	1.7	/ [a]
Histidine (His)	2.2	1.2	3.2	2.3	2.3	1.3
Lysine (Lys)	2.7	1.7	8.2	3.6	6.4	2.3
Arginine (Arg)	3.2	0.8	7.2	12.0	7.8	6.7
Aspartic acid (Asp)[b]	5.5	8.0	8.5	10.0	11.9	6.6
Glutamic acid (Glu)[c]	33.8	54.8	13.9	21.0	19.7	9.9

[a] Tryptophan was not determined, because of degradation under acidic conditions. [b] Asparagine (Asn) is included. [c] Glutamine (Gln) is included.

For example, soybean meal protein was obtained in almost 90% yield under very mild extraction conditions (*e.g.* 25-120 °C, pH 10), whereas under similar conditions rather low protein yields were obtained from sugar beet pulp (60%) or microalgae (18%)[48] due to a more rigid cell wall structure, lower protein solubility and the presence of pectin, oil or phenolic compounds. The extraction efficiency can be improved by using enzymes such as pectinases, cellulases or alkaline proteases, which assist in the hydrolytic degradation of these cell wall components.[20,39,51] Chemical and mechanical treatments such as ammonia fiber expansion (AFEX) or ball milling have been applied to facilitate solvent permeation through the cell wall.[52,54–56] Recently, even a dry platform based on a combination of ultrafine milling and electrostatic separation has been designed for isolating proteins out of biomass.[57] Nevertheless, none of these promising techniques has been developed for large-scale protein extraction yet, and innovative engineering approaches are required in order to realize new bio-based product manufacturing.

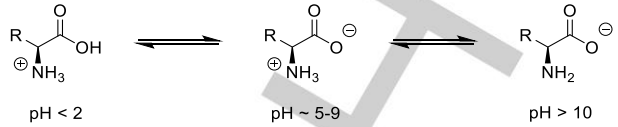
Next, proteins are hydrolyzed into oligopeptides and free amino acids, which can be handled as substrates in (bio)chemical conversion technologies. Complete hydrolysis is achieved under highly acidic conditions (*e.g.* 6 M HCl, 110 °C, 24 h). However, tryptophan, tyrosine, serine and threonine are (partially) degraded under these conditions, whereas glutamine and asparagine are deamidated to glutamic acid and aspartic acid, respectively.[58–60] Near-complete hydrolysis is also possible under highly alkaline conditions (*e.g.* 5 M NaOH, 100 °C, 24 h),[39] but lysine, cysteine and threonine are degraded under these conditions and amino acids are highly susceptible to racemization. Nevertheless, both approaches have environmental drawbacks[61] such as the risk of acid or base leakage and salt waste generation upon neutralization, and require specific reactor designs; the application potential is therefore limited to analytical purposes.[58–60] Enzymatic protein hydrolysis, eventually in combination with a mild chemical hydrolysis, has been proposed as an alternative. Since proteases often show a high level of specificity towards

certain peptide bonds, a high degree of hydrolysis is only achieved by combining exo- and endoproteases. Nevertheless, such a high substrate specificity can be beneficial when targeting a particular peptide bond (section 4). The economic feasibility of enzymatic hydrolysis can be improved by immobilizing proteases on a solid support,[62] thereby protecting them against autolysis and enhancing the recovery.[39,58,63] For instance, Bruins and coworkers developed a two-step procedure for the extraction of glutamic acid from wheat gluten. The proteins were hydrolyzed first by a cocktail of exo- and endopeptidases under mild conditions (*e.g.* pH 6-7, 40-55 °C, 24 h) in order to solubilize > 90% of the protein content into peptides and free amino acids. In the second step this mixture was treated under diluted acidic conditions (*e.g.* 1 M HCl, 95 °C, 48 h) to induce profound peptide hydrolysis and glutamine deamidation, yielding about 70% free glutamic acid and 10% pyroglutamic acid, as a result of spontaneous intramolecular condensation of both glutamine and glutamic acid at higher temperature. The overall glutamic acid yield was increased to 80% by hydrolyzing the lactam moiety in pyroglutamic acid under highly acidic or alkaline conditions.[49] About 55% of the total amino acid content was liberated *via* this two-step procedure; besides glutamic acid also aspartic acid, alanine, valine, leucine and isoleucine were obtained in very high yields.

Subcritical water hydrolysis (*e.g.* 100-374 °C, 0.10-22 MPa) provides another strategy to convert proteins to oligopeptides and free amino acids. Under these conditions the ionic product of water increases and hence hydrolysis will occur to a higher extent. Although this approach can be considered as green and environmentally friendly due to the absence of additional reagents, the high energy input and the need for pressure-resistant equipment makes this technique less attractive for large-scale applications. Moreover, free amino acids are susceptible to decomposition upon treating them for a long time at high temperature in water.[64,65]

2.3 Amino acid separation

Protein hydrolysates contain besides amino acids also inorganic salts and small amounts of other biomass constituents.[66] The isolation of single amino acids out of these diluted aqueous mixtures is the most challenging step in the valorization process, predominantly because of their pH-dependent charge behavior in water (Scheme 2).[8] In principle, amino acids can be separated based on differences in physicochemical properties such as size, hydrophobicity and charge characteristics, or combinations thereof.[8] Traditional separation techniques such as crystallization at the isoelectric point,[36] anti-solvent precipitation,[67,68] reactive extraction[69–71] and membrane filtration[72] are useful as a downstream processing step in the fermentative production of amino acids, but are inefficient for isolating single amino acids out of a complex aqueous mixture. Ion-exchange chromatography is more appropriate for that purpose.[68] However, a series of ion-exchange columns is required to obtain pure amino acids and large amounts of chemicals are consumed during column regeneration, which is accompanied with high waste loads[2,21] and high waste-liquor treatment costs. Therefore, this expensive technique is rather limited to the purification of high-value fine chemicals and for analytical purposes.



Scheme 2. Charge behavior of α-amino acids in aqueous media with different pH.

Recently, several techniques have been developed for the fractionation of amino acid mixtures, thereby exploiting differences in physicochemical properties. Liquid-liquid extraction might seem inappropriate at first sight because amino acids possess pH-dependent functional groups which render them rather hydrophilic over the entire pH range (Scheme 2);[66] hence, the solubility of most amino acids in water-immiscible solvents will be negligible.[68] However, the extraction efficiency can be improved by the addition of lipophilic acidic surfactants such as dinonylnaphthylsulfonic acid[73] and di-(2-ethylhexyl)phosphoric acid to the biphasic mixture (Figure 2).[66,68] These surfactants are more acidic than most amino acids ($pK_a \approx 2$), hence at pH 2-5 they will form ion-pair complexes with amino acid cations, which can be readily transferred to a water-immiscible organic solvent. Such a reactive extraction is particularly suitable for neutral and basic amino acids, but not for acidic amino acids.[66,68,73] In this way some amino acids can also be separated based on small differences in hydrophobicity. For instance, dinonylnaphthylsulfonic acid enhances the separation of alanine and glycine in a water (pH 3.5)-toluene biphasic mixture (separation factor α = 11.9).[73] Phenylalanine was extracted with higher efficiency compared to tyrosine - 85% vs. 57% - from an aqueous solution at pH 5 to *n*-octane with di-(2-ethylhexyl)phosphoric acid, which can be attributed to the presence of a phenolic moiety in tyrosine.[66] Upon application of reactive extraction with di-(2-ethylhexyl)phosphoric acid on a cottonseed meal hydrolysate, most of the hydrophobic amino acids were successfully transferred to the organic phase, whereas the hydrophilic ones were partially retained in the aqueous phase, together with inorganic salts and residual reducing sugars.[66]

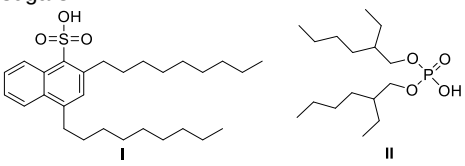


Figure 2. Lipophilic acidic surfactants applied for reactive extraction of amino acids from aqueous solutions: dinonylnaphthylsulfonic acid (**I**) and di-(2-ethylhexyl)phosphoric acid (**II**).

Another strategy relies on ionic liquid- or zwitterion-based aqueous biphasic systems (ABS) with a high salting-out tendency, which are easily obtained either by mixing hydrophobic ionic liquids with hydrophilic amino acids,[74] or by combining

hydrophobic zwitterions[75] or even ethyl lactate[76] with an inorganic salt. Because of the high water content in both phases, these systems are able to induce the separation of aliphatic amino acids and aromatic ones (Figure 3**Error! Reference source not found.**). In ionic liquid-based ABS, aromatic amino acids have a strong tendency to be transferred to the ionic liquid-rich phase, whereas aliphatic amino acids remain in the other phase; the extraction efficiency is predominantly related to the salting-out aptitude of the aliphatic amino acids. For instance, in a lysine hydrochloride + tetrabutylphosphonium bromide ABS 45-85% of the aromatic amino acids were extracted into the ionic-liquid-rich phase while even > 95% of the aliphatic amino acids were retained in the opposite phase after only one step.[74] Ionic liquids can also be applied as an auxiliary in polymer-salt ABS to increase the polarity of the organic phase. For instance, a 2- to 4-fold increase of phenylalanine in the organic phase was observed upon addition of 1-butyl-3-methylimidazolium acetate to a polyethylene glycol 600 + NaH_2PO_4 ABS.[77] In zwitterion-based ABS, the extraction efficiencies are related to the hydrophobicity of the zwitterion. When a glycine-tryptophan mixture was treated in an *N*,*N*,*N*-tripentyl-3-sulfonyl-1-propaneammonium + K_3PO_4 ABS, 84% of tryptophan was extracted to the zwitterion-rich phase and 67% of glycine was retained in the opposite phase.[75] Although ABS are promising media for amino acid fractionation, their performance on a real fermentation broth or a protein hydrolysate has not been reported yet; hence, the influence of residual biomass constituents, such as carbohydrates and phenolic compounds, on the extraction efficiency is still unknown.

A third approach consists of the selective adsorption of amino acids on a solid porous material. For instance, De Vos and coworkers demonstrated that aromatic amino acids are efficiently adsorbed on the metal-organic framework MIL-140C. This hydrophobic and water-stable material is constructed of infinite Zr-oxide chains consisting of ZrO_7 polyhedra that are connected in six directions through 4,4'-biphenyldicarboxylate linkers to define triangularly shaped microporous one-dimensional channels.[78] The driving force for adsorption is provided by π-π stacking interactions between the aromatic moieties of phenylalanine, tyrosine and tryptophan, and the organic linker in the material. Moreover, MIL-140C shows a different affinity for aromatic amino acids (*viz.* tryptophan > tyrosine > phenylalanine), which is attributed to additional hydrogen bond interactions between the indole and phenol moieties and the Zr-oxide chain. MIL-140C exhibits uptakes of 15 wt% for tryptophan and 20 wt% for phenylalanine. The desorption proceeds easily in aqueous ethanol and the adsorbent remains stable after several recycling steps. Therefore, the MIL-140C adsorbent shows high potential for the work-up of single aromatic amino acids from fermentation broths and it is quite promising for the fractionation of protein hydrolysates into aromatic and non-aromatic amino acids. However, MIL-140C has to deal with considerable co-adsorption of glutamic acid and aspartic acid.[79] Also here the influence of other biomass constituents on the performance should be investigated, because MIL-140C has already been demonstrated to be an efficient adsorbent for the separation of phenolics in aqueous media.[78]

Anti-solvent precipitation allows to fractionate amino acids based on their hydrophobicity. The solubility of an amino acid is dependent on the solvent composition and the presence of other amino acids in the medium. For instance, the solubility of a polar amino acid in water can increase due to the presence of other polar amino acids,[80] and the relative solubility of amino acids decreases with a different selectivity in a water-alcohol system.[81] Based on these properties protein hydrolysates can be fractionated by the addition of ethanol: almost all amino acids started precipitating below their maximal solubility in water and at high ethanol concentrations (*e.g.* 80 wt%) > 75% of the polar amino acids were precipitated, whereas > 80% of the hydrophobic ones remained in solution. Furthermore, the overall solubility of hydrophobic amino acids in ethanol increases due to intermolecular interactions. Consequently, a high amino acid concentration or a large fraction of hydrophobic amino acids will result in a more efficient separation between polar and hydrophobic amino acids at very high ethanol concentrations (> 95%).[67]

Finally, electrodialysis allows to fractionate amino acids according to their pH-dependent charge behavior in water; this technique is nowadays the most promising and closest to maturity.[72,82–85] A typical set-up contains an alternating series of cation- and anion-exchanging membranes in an electric field. The electrical potential difference over these membranes provides the driving force for the separation (Figure 4). In this way a protein hydrolysate at neutral pH can be separated in acidic (negatively

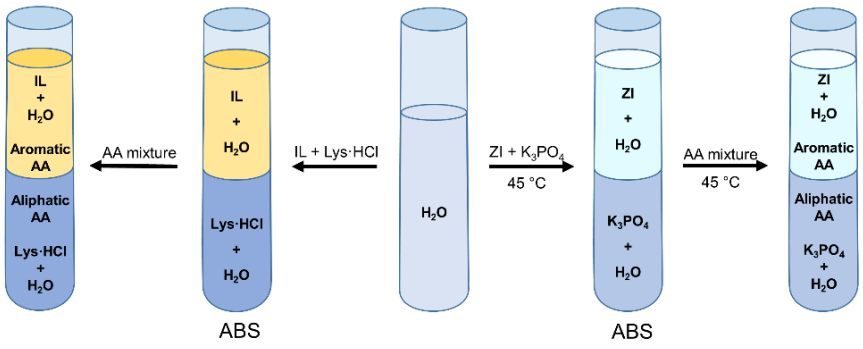


Figure 3. Aqueous biphasic systems (ABS) containing either a hydrophobic ionic liquid (IL) and lysine hydrochloride (left), or a hydrophobic zwitterion (ZI) and K_3PO_4 (right) for the separation of aliphatic and aromatic amino acids (AA).[74,75]

charged), basic (positively charged) and neutral amino acid fractions with an overall recovery > 80%.[82] Further separation to single amino acids is, however, challenging because the isoelectric points of amino acids in one fraction are nearly similar, *e.g.* 2.77 for aspartic acid and 3.22 for glutamic acid.

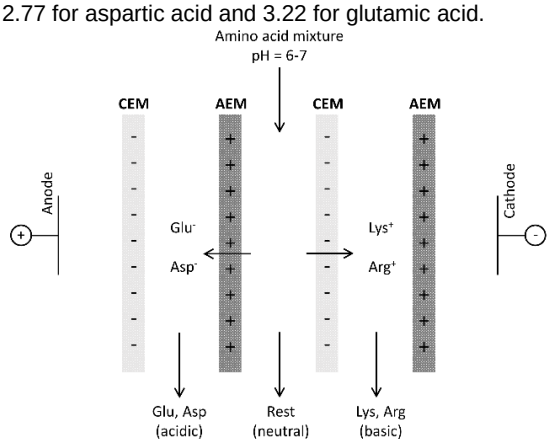


Figure 4. Electrodialysis set-up for the separation of a protein hydrolysate into acidic, neutral and basic amino acid fractions.[85] CEM: cation-exchange membrane; AEM: anion-exchange membrane.

Two approaches allow to overcome this limitation:

(i) One or more amino acids are converted in a reversible manner to an intermediate product with different physicochemical properties, *e.g.* charge or solubility. For instance, when a mixture of aspartic acid and glutamic acid was incubated at > 100 °C, the latter was converted to pyroglutamic acid by intramolecular condensation. Excellent yields of pyroglutamic acid were obtained in aqueous solutions (86%; 3 h at 120 °C) as well as in a melt (> 99%; 45 min at 150 °C) of both amino acids. Aspartic acid remained intact,[49] because cyclisation to the β-lactam derivative is thermodynamically disfavored and deamination to fumaric acid is negligible under acidic conditions at 150 °C.[86] Subsequently, aspartic acid can be separated with high purity by precipitation, due to its low solubility in water compared to pyroglutamic acid (respectively 5.39 g L^{-1} and 476 g L^{-1}). After subsequent hydrolysis of pyroglutamic acid in concentrated acid (*e.g.* 2 M H_2SO_4), aspartic acid and glutamic acid were recovered with overall yields up to 80% and 99%, respectively.[49]

(ii) An alternative approach involves a non-reversible modification or defunctionalization of one or more amino acids to valuable end products that are readily separated from each other, or from unreacted amino acids. In this way extensive downstream processing can be avoided, which will enhance the economic feasibility of the valorization process. In the next sections various (bio)chemical conversion technologies for amino acids will be discussed (Figure 1). Depending on the conversion technology and the target products, the substrate scope comprises either one amino acid,[87–91] a selected mixture of amino acids[92] or the entire protein hydrolysate.[93]

3 Bio-based materials derived from proteins and oligopeptides

In the previous part it has been demonstrated that several protein-rich biomass streams should be considered as excellent sources of amino acids for the production of commodity and fine chemicals. However, proteins and oligopeptides can also be applied as raw materials in the synthesis of bio-based and/or biodegradable materials, provided that there is no competition with food or feed applications; hence, gluten, whey protein and gelatin will not be considered for that purpose. Moreover, the direct use of proteins is attractive since hydrolysis to amino acids and related separation issues are avoided. Although this field has already been reviewed extensively,[94–99] the aim is only to highlight some relevant examples on the incorporation of proteins into biomaterials, thereby comparing the assets and drawbacks of each approach.

A first approach involves the use of proteins which are entirely composed of one amino acid, *e.g.* poly-(γ-glutamic acid) or poly-(ε-lysine). Due to their uniform structure these polymers have far more interesting and controllable properties than proteins extracted from biomass. Poly-(γ-glutamic acid) is industrially produced by fermentation from carbohydrates and NH_3 using *Bacillus subtilis* (Figure 5, **I**). After esterification of the α-carboxylic acid groups with alkyl halides, the polymer shows comparable properties to nylons.[100] Similarly, poly-(ε-lysine) has potential applications *e.g.* as food preservative, dietary agent, antimicrobial agent, in medicine, drug delivery *etc.* (Figure 5, **II**). Alternatively, cyanobacteria are able to synthesize cyanophycin, a protein that consists of a poly-(α-aspartic acid) backbone in which each residue is linked to an arginine residue *via* the β-carboxylic acid moiety (Figure 5, **III**). Poly-(α-aspartic acid) is obtained upon hydrolysis of arginine residues, and has potential applications as *e.g.* detergent, ingredient for cosmetics, fertilizer, adsorbent resin *etc*.[1,101] However, the production and applications of poly-(ε-lysine) and poly-(α-aspartic acid) have not been commercialized yet, because the fermentative production processes still suffer from low productivity and high cost.[102,103]

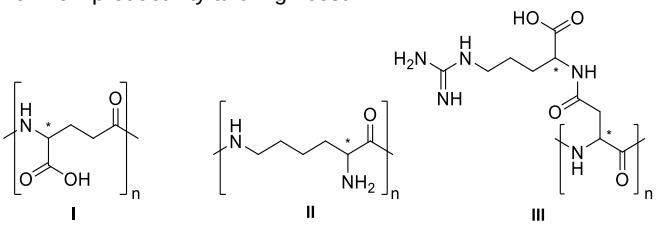


Figure 5. Molecular structures of poly-(γ-glutamic acid) (**I**), poly-(ε-lysine) (**II**) and cyanophycin (**III**).

In a second approach, proteins are applied as such, without any pre-treatment, in the production of bio-based films which have applications as packaging materials, coatings *etc*. Both wet and dry processing techniques have been developed. In the former technique the proteins are first dissolved in an organic solvent and the biomaterial is obtained by casting the polymer solution and drying. Unfortunately, large amounts of solvents are required and

the production process is time-consuming. The dry processing technique based on mixing proteins with additives and producing the biomaterial *via* extrusion or molding[97] is therefore more preferred. Plasticizers (*e.g.* glycerol) are essential to decrease intermolecular interactions, in particular hydrogen bond interactions, and to increase the flexibility of the film, whereas cross-linking agents (*e.g.* formaldehyde, glutaraldehyde) are required to obtain a 3D polymer network and to improve the mechanical properties of the film due to its high water sensitivity.[97,104–107] However, rather high amounts of additives (*e.g.* 30-40% plasticizers) are required and there is also limited control on the degree of cross-linking and hence on the properties of the film. When using formaldehyde as a cross-linking agent, hydroxymethyl, dimethylene-ether and methylene linkages are formed between the primary amino groups in lysine residues and the guanidine groups in arginine residues. The relative amount of these linkages is pH-dependent;[108] hence, the properties of the film can be tuned by controlling the pH. The amount of external additives can be reduced by utilizing other biomass constituents as well, which has been demonstrated for soy flour (containing about 55% proteins and 32% carbohydrates).[109] The carbohydrates were oxidized first with hydrogen peroxide (H_2O_2) at pH 2 to aldehydes and polycarboxylic acids, which were used next to cross-link with the proteins *via* Maillard-type reactions. Micro-fibrillated cellulose (5%) was added afterwards as a plasticizer to obtain a polymer with good thermal and mechanical properties. Although the use of soy flour is competitive with food applications, this strategy shows potential for other biomass waste streams which also contain both proteins and carbohydrates. The water sensitivity of these films can be reduced by increasing the hydrophobicity of proteins, either by incorporating a hydrophobic co-polymer, or by chemically modifying the protein *via* graft polymerization[98] with *e.g.* acrylonitrile[110] or methacrylate monomers.[111] However, some limitations still have to be overcome before commercialization is viable, *e.g.* low control over grafting during the radical polymerization, large amount and difficult removal of the catalyst.[98]

The last approach consists of producing polymers that are prepared from two pre-polymers, and in which one of them is substituted by a protein or a derivative thereof. Oligopeptides contain multiple active hydrogens (*viz.* amine and alcohol groups) and are thus potential polyamines and polyols for the synthesis of polyurethanes (PUR). This strategy has been demonstrated by using defatted soy flour for replacing up to 20% of the conventional poly(ether polyol) in the synthesis of water-blown rigid PUR foams.[112] Since the cost of conventional polyols is about 1,300-1,700 € ton^{-1}, the use of soy-based polyol is much more cost-efficient (about 300 € ton^{-1}),[113] especially because these bio-based foams have similar or even improved properties compared to the petroleum-based foam.

4 Amino acids as direct precursors to value-added chemicals

The production of bio-based chemicals from amino acids benefits from the highly functionalized carbon backbone, in particular the presence of an amine moiety and chiral centers. Consequently, a range of value-added chemicals can be obtained by either a subtle modification or a defunctionalization of amino acids. In this way one may even produce chemicals which are currently not directly available from petrochemical feedstocks or require energy-intensive multi-step synthesis methods involving hazardous solvents and reagents. In addition, the challenging isolation of amino acids is circumvented because the pH-dependent charge behavior of amino acids will disappear. In the following sections state-of-the-art enzymatic, chemical and chemocatalytic strategies for modification and defunctionalization of amino acids will be discussed.[63,114,115]

4.1 Modification of functional groups

4.1.1 Reduction to amino alcohols

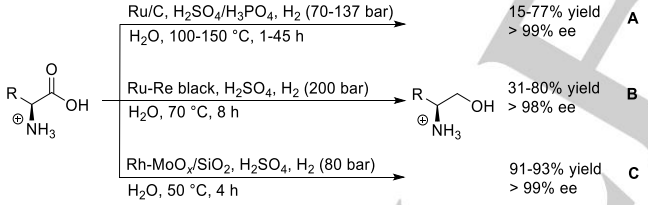
The reduction of the carboxylic acid moiety in α-amino acids offers an attractive route towards optically active β-amino alcohols.[34] These compounds have numerous applications, a.o. as chiral auxiliaries in asymmetric synthesis (*e.g.* pseudoephedrine),[116] building blocks for pharmaceuticals and agrochemicals (*e.g.* ethambutol, nelfinavir),[117,118] and polymer precursors (*e.g.* lysinol).[119]

Both free amino acids and their alkyl ester derivatives can be used for the synthesis of bio-based amino alcohols; the atom economy for this transformation is excellent for both carbon and nitrogen. A first strategy involves a treatment with metal hydride reagents such as lithium aluminum hydride ($LiAlH_4$)[120,121] or sodium borohydride ($NaBH_4$).[122,123] For instance, several amino acid methyl esters were converted using $NaBH_4$ (5 equiv.) in tetrahydrofuran under reflux conditions and the corresponding amino alcohols were obtained in 50-95% yield.[123] Other reagents have been reported for the reduction of free amino acids, but in some cases a protecting group on the amine moiety is required for reasons of selectivity: either borane-methyl sulfide in the presence of boron trifluoride etherate,[124,125] or $NaBH_4$ in combination with H_2SO_4,[126] I_2,[127] trimethylchlorosilane,[128,129] or 1,1-carbonyl-diimidazole.[130] Although these methods proceed under mild conditions (*e.g.* < 80 °C and at atmospheric pressure) and provide the desired amino alcohols in good to high yields, they are typically performed in hazardous tetrahydrofuran thereby using the reducing agent in large excess, resulting in a high waste load. Moreover, metal hydride reagents are expensive and often difficult to handle because of their sensitivity to moisture and air.

Another, more viable strategy relies on transition metal-catalyzed hydrogenation, where hydride species are produced *in situ* by the dissociation of molecular hydrogen (H_2) on the metal surface. In this way, water is produced as the only by-product and the reduction proceeds with a higher overall atom economy. However, the reaction generally requires higher temperatures and pressures, thereby increasing the risk of racemization and other

side reactions. Complementary methods have been developed for the hydrogenation of free amino acids and their ester derivatives.

When the hydrogenation of amino acid esters was carried out with homogeneous Ru catalysts,[131] Rh/Pt oxide (Nishimura catalyst),[132] Raney Ni[133] or a supported Cu catalyst,[134–136] amino alcohols were obtained in good to excellent yields and with very high enantiomeric excess (ee). For instance, L-phenylalaninol was produced in about 70% yield and with > 99.8% ee from methyl L-phenylalaninate over a $Cu/ZnO/Al_2O_3$ catalyst.[134] However, these methods were performed in organic solvents under very high pressures (*e.g.* ranging from 40-50 up to 350 bar H_2 at 100 °C) and the homogeneous Ru catalyst was only able to convert substrates with a protecting group on the amine moiety. The first attempts to the hydrogenation of free amino acids in aqueous media with heterogeneous Ru and Ni catalysts were also performed at very high pressures (*e.g.* 200 bar H_2 at 100 °C) and long reaction times (up to 30 h). For instance, under these conditions L-alanine was converted by Ru black to L-alaninol with 40% yield and 95% ee.[137] Bimetallic Ru-Re catalysts, either unsupported[138] or immobilized on carbon,[139] operate under slightly milder conditions (*e.g.* 150-200 bar H_2 at 80-120 °C) and amino alcohols were produced in 32-80% yield and with > 98% ee (Scheme 3, route **B**). The oxophilic Re co-catalyst facilitates the reduction by increasing the electrophilic character of the carbonyl group for a hydride attack. However, catalyst sintering was observed as a major disadvantage. Alternatively, the activity of Ru catalysts can be increased substantially under highly acidic conditions, *e.g.* L-alaninol was obtained in 91% yield and with 99.2% ee when the hydrogenation of L-alanine was performed with Ru/C in 0.29 M H_3PO_4 at 100 °C under 70 bar H_2 for 6 h (Scheme 3, route **A**).[140]



Scheme 3. Catalytic hydrogenation of amino acids to amino alcohols using Ru/C (route **A**),[119,140,141] Ru-Re black (route **B**)[138] and $Rh\text{-}MoO_x/SiO_2$ (route **C**).[142,143]

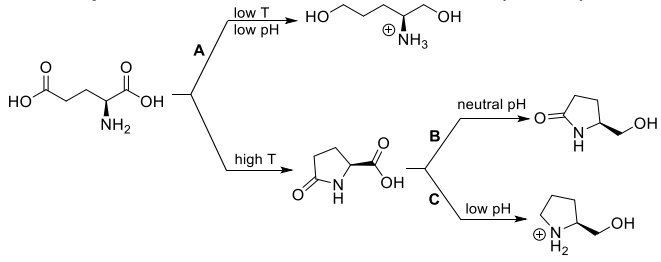
The reduction of a carboxylic acid is thermodynamically more favorable compared to a carboxylate anion and the electrophilic character of the carbonyl carbon is also increased by the neighboring electron-withdrawing groups and by intramolecular hydrogen bond interactions with the protonated amino group.[140,142,143] Since the carboxylic acid moiety in α-amino acids has rather acidic properties ($pK_a \approx 2$) and the pH of the reaction medium increases upon accumulation of amino alcohols, a high concentration of mineral acid is often required to keep the carboxylic acid in a protonated state. Besides, a deuterium incorporation study revealed that L-alaninol reached its maximum yield at full conversion, while racemization was more pronounced at longer reaction times. The chirality of the amino acid can thus be retained at short reaction times and sufficiently low temperature.

Finally, Tomishige and coworkers identified $Rh\text{-}MoO_x/SiO_2$ (4 wt% Rh, Mo/Rh = 1/8) as a highly active bimetallic catalyst for the reduction of amino acids at much lower temperatures (< 70 °C) and pressures (80 bar H_2) compared to the Ru-based systems (Scheme 3, route **C**).[142,143] For instance, aliphatic amino acids were successfully converted to the corresponding amino alcohols with > 90% yield and > 99.9% ee after 4 h at 50 °C.[142] Metallic Rh and partially reduced MoO_x species are expected to be in close proximity and the adsorption of amino acids is facilitated by hydrogen bond interactions between MoO_x species and the carboxylic acid group. Furthermore, the use of a supported catalyst is beneficial in terms of activity and stability. Prolonging the reaction time did not affect the selectivity or the chirality, indicating that racemization and C-O hydrogenolysis did not occur under these conditions. Recently, De Vos and coworkers adapted this Rh-based catalytic system in order to extend the scope towards more challenging amino acids. By increasing the temperature to 80 °C and prolonging the reaction time, the majority of the natural amino acids – except for tryptophan, glutamine and asparagine because of degradation under acidic conditions – were converted to the corresponding amino alcohols in good to excellent yields; even glutamic acid was unambiguously reduced to glutamidiol with 77% yield. However, racemization of amino alcohols and C-O hydrogenolysis to the corresponding amines were more pronounced under these conditions. Moreover, the aromatic moieties in phenylalanine and tyrosine were completely reduced to their saturated analogs, but this side reaction has been observed for Ru-based catalysts as well.[139,144] Poisoning of the Rh catalyst by cysteine and methionine was avoided by applying an oxidative pre-treatment with performic acid, in order to convert the S-containing thiol and thio-ether groups to inert sulfonic acid and sulfone groups, which do not possess lone pairs anymore.[145]

The synthesis amino alcohols can be an interesting route in the valorization of the entire pool of natural amino acids. Due to the retention of chirality, these amino alcohols are excellent building blocks for various applications. However, the hydrogenation of crude protein hydrolysates is complex due to the presence of other biomass constituents. As a proof of concept De Vos and coworkers applied their procedure involving a $Rh\text{-}MoO_x/SiO_2$ catalyst for the hydrogenation of a bovin serum albumin hydrolysate.[145] The catalytic activity was reduced compared to the hydrogenation of single amino acids due to the presence of degradation products generated during the oxidation with performic acid and subsequent hydrolysis (*e.g.* tryptophan) and also because of competitive adsorption of amino acids on the catalyst surface.[141] Nevertheless, amino alcohols were still obtained with 88% selectivity at 90% conversion after 48 h.[145]

In view of potential applications, fractionation of aqueous amino acid mixtures prior to hydrogenation is recommended. Amino alcohols derived from acidic and basic amino acids are potential polymer building blocks. However, the selective hydrogenation of L-glutamic acid to L-glutamidiol or (*S*)-2-amino-1,5-pentanediol is challenging in comparison with other amino acids due to the presence of an additional carboxylic acid group

in the side chain (Scheme 4, route **A**). Moreover, the conversion L-glutamic acid to L-pyroglutamic acid is a competitive side reaction that proceeds spontaneously at higher temperature and especially under acidic conditions. Interestingly, the selectivity can be controlled by adjusting the acidity of the medium. For instance, when the hydrogenation of L-pyroglutamic acid was performed with Ru/C at 70 bar H_2 for 1 h, L-pyroglutaminol was obtained with 85% selectivity at 90% conversion under neutral conditions (route **B**), whereas L-prolinol was obtained with 98% selectivity at 98% conversion in an acidic medium (route **C**).[146,147]



Scheme 4. Ru-catalyzed hydrogenation of L-glutamic acid to L-glutamidiol (route **A**), L-pyroglutaminol (route **B**) and L-prolinol (route **C**).[138,146,147]

The reduction of basic amino acids proceeds more easily. For instance, lysine was hydrogenated to lysinol in 50-70% yield using Ru/C and the amino alcohol was incorporated as a hardener into an epoxy thermoset together with a bisphenol A diglycidyl ether (BADGE, Scheme 5).[119] Upon comparison with a conventional epoxy thermoset prepared from diethylenetriamine the bio-based material showed similar properties (*e.g.* tensile strength, compression modulus *etc.*) except for a slightly lower thermal stability. It is conceivable that similar polymers can be prepared from ornithine, obtained by enzymatic hydrolysis of arginine.[148]

4.1.2 Modification of the α-amino group

The acidic amino acids aspartic acid and glutamic acid have been exploited as polymer building blocks.[100] Recently, De Vos and coworkers demonstrated the potential of glutamic acid dimethyl ester as a bio-based substitute for conventional aromatic diacid monomers such as isophthalic acid in the synthesis of alkyd resins,[149] which have applications in inks and paints. Reducing the reactivity of the α-amino group in this substrate by acylation with palmitoyl chloride or alkylation with hexadecyl bromide is recommended to obtain a polymer with a high molecular weight, otherwise pyroglutamic acid can be obtained at high temperature and incorporated as a chain stopper. Moreover, modification of the primary amine to an inert amide or a secondary amine is beneficial to limit discoloration of the resin.

4.2 Elimination of functional groups

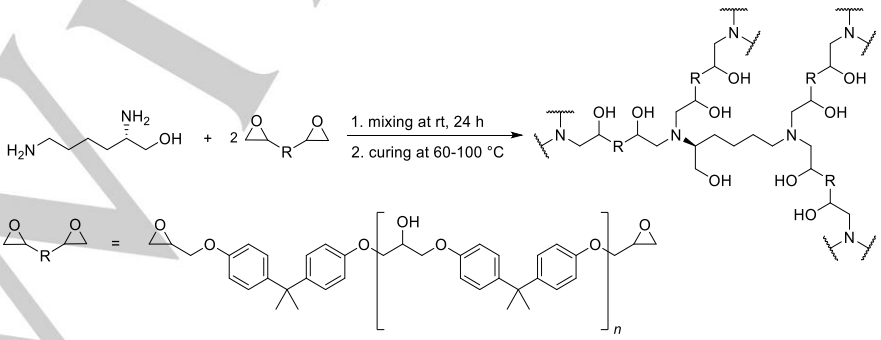
The selective removal of one functional group on the α-carbon in an amino acid, *viz*. elimination of either CO_2 (decarboxylation) or NH_3 (deamination), provides access to a variety of valuable products such as (cyclic) amides, (di)amines, nitriles, (di)carboxylic acids *etc*. which do not behave as zwitterions in water anymore. Consequently, applying this approach to a mixture of similar amino acids may facilitate product separation by traditional techniques such as precipitation, distillation or extraction.

4.2.1 Decarboxylation of amino acids

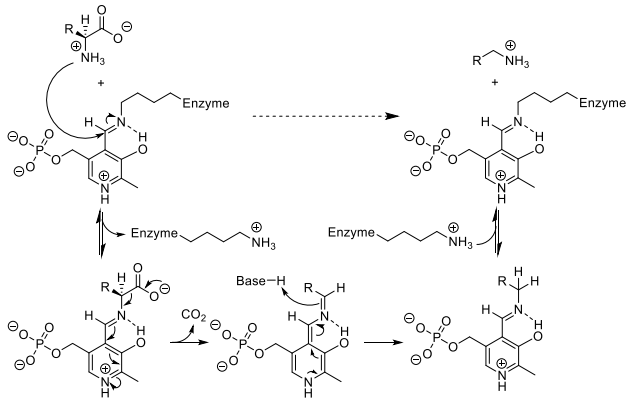
The decarboxylation of amino acids provides a direct route towards bio-based nitrogenous compounds: either primary (or secondary) amines, or nitriles when the elimination of CO_2 occurs simultaneously with the oxidation of the α-amino group. Moreover, decarboxylation is also a useful tool to convert pyroglutamic acid to 2-pyrrolidone and N-alkylated derivatives thereof. The elimination of CO_2 can be facilitated by enzymes, homogeneous and heterogeneous catalysts in which transition metals or even relatively simple organic molecules play a key role in terms of activity.

4.2.1.1 Enzymatic decarboxylation

The non-oxidative decarboxylation of amino acids to primary amines can be facilitated by decarboxylases. These enzymes employ reactive carbonyl compounds such as pyridoxal 5'-phosphate (PLP; vitamin B_6) or a pyruvoyl moiety as a cofactor in the active site. The mechanism relies on the generation of a Schiff base adduct by condensation of the carbonyl compound with the α-amino group in the substrate. In PLP-dependent enzymes an azomethine ylide is generated upon decarboxylation of the Schiff base adduct and this intermediate is stabilized by electron delocalization in a conjugated system, in which the pyridinium moiety serves as a temporary electron sink (Scheme 6).[150]



Scheme 5. Synthesis of an epoxy thermoset from lysinol and a bisphenol A diglycidyl ether (BADGE).[119]



Scheme 6. Mechanism for the pyridoxal 5'-phosphate-catalyzed decarboxylation of α-amino acids in enzymes.

The aromaticity of the latter is re-established upon electron rearrangement and protonation of the carbanion at the α-carbon. Although PLP-dependent enzymes are also involved in the racemization and transamination of amino acids, the product selectivity is mainly guided by stereo-electronic interactions between the Schiff base adduct and amino acid residues of the surrounding protein matrix.[151,152]

These enzymes have been exploited in the bio-based production of γ-aminobutyric acid (GABA) and cadaverine from glutamic acid and lysine, respectively.[153] GABA serves as a neurotransmitter in the human brain and is therefore relevant for pharmaceutical applications.[154] This ω-amino acid can be produced at high concentrations and in 77% yield in a fermentation process using the *E. coli* NBRC 3806 strain, even in the absence of PLP or a buffered process medium. Moreover, when GABA was isolated from the fermentation broth and heated at 200-240 °C for a short time, the intramolecular condensation to 2-pyrrolidone proceeded with 96% yield.[155] In another study, this lactam was obtained in the same yield by contacting GABA with a molar excess of Al_2O_3 in toluene under reflux conditions.[156]

Cadaverine or 1,5-pentanediamine has potential applications as a building block in polyamide and polyurethane synthesis.[157] For instance, Clark and coworkers developed a copolymerization process to obtain self-blowing rigid polyurethane foams from cadaverine and a sorbitol-derived bis-carbonate under solvent-free conditions, thereby avoiding the use of toxic isocyanates.[158] The enzymatic decarboxylation of lysine is therefore highly attractive, because such a direct pathway to the C_5 diamine has not been established from fossil resources. Lysine decarboxylase operates under mild conditions, typically at pH 6 and 37 °C, and its activity can be maintained after immobilization by entrapment in calcium alginate,[87] by covalent grafting on a biopolymer[159] or by preparing cross-linked enzyme aggregates (CLEAs).[160] For instance, lysine decarboxylase immobilized on poly-3-hydroxybutyrate granules produces cadaverine in 75-80% yield, even after 5 cycles. As an alternative to the direct bioconversion using isolated enzymes, cadaverine can also be produced by fermentation using whole cell biocatalysts.[161] Several cadaverine over-producing micro-organisms have been developed by genetic engineering, in particular by introducing the genes encoding for lysine decarboxylase in recombinant *E. coli* and *C. glutamicum* strains. The microbial productivity has been improved by metabolic engineering of central supporting anabolic pathways to generate lysine in the cell, and by increasing the efflux of cadaverine to the fermentation medium.[162–164] The supply of the PLP cofactor constitutes another bottleneck in the process,[165] which can be eliminated by enhancing the enzyme's affinity for PLP[166] or by introducing pyridoxal kinase, which allows to generate PLP *in situ* from the less expensive pyridoxal.[167] Since the pH increases upon accumulation of the diamine in the medium, continuous neutralization is required to maintain the enzymatic activity in the optimal range. Alternatively, the reaction can be performed with enzymes that are able to operate under alkaline conditions.[168] A significant improvement to control the pH of the medium was recently achieved by combining the enzymatic decarboxylation of lysine with the fermentation of succinic acid from glucose and CO_2. The simultaneous production of cadaverine and succinic acid – both are monomers of polyamide-5,4 – was facilitated by a recombinant *E. coli* strain.[169] By balancing the rates of both reactions succinic acid and cadaverine can be produced in > 20 g L^{-1} without pH adjustments and exogenous supply of CO_2. Although glucose is a typical carbon source in fermentation processes,[170] cadaverine over-producing micro-organisms have been developed by metabolic engineering to grow on other, preferably non-edible biomass constituents such as starch,[171] galactose,[172] cellobiose[173] and xylooligosaccharides.[174] Finally, product purification and reuse of the biocatalysts can be facilitated by immobilizing the cells on a solid support such as barium alginate.[175]

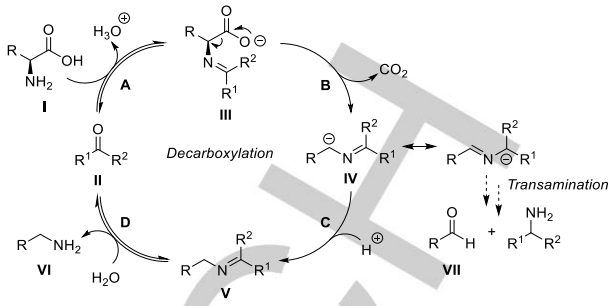
Sanders, Scott and coworkers demonstrated the potential of enzymatic transformations for the valorization of cyanophycin (Figure 5, **III**). After hydrolysis and electrodialytic separation of aspartic acid and arginine, an enzymatic cascade consisting of arginase[148] and ornithine decarboxylase[176] was designed to convert arginine into putrescine or 1,4-butanediamine. Besides, aspartate-α-decarboxylase has been used for the bio-based production of β-alanine from aspartic acid.[177] This research group showed also that enzymatic decarboxylation is an efficient tool for the separation of amino acids with a similar isoelectric point. The high activity and high substrate specificity of amino acid decarboxylases enables the selective transformation of a particular compound into a product with a different charge behavior. For instance, a mixture of glutamic acid and aspartic acid – the acidic amino acid fraction obtained by electrodialysis – can be separated by using glutamic acid α-decarboxylase.[178] Process intensification has been achieved by immobilizing the enzyme in solid porous materials,[50] which in turn can be embedded in a mixed matrix membrane system.[91] Similarly, lysine decarboxylase was applied in the separation of the basic amino acids lysine and arginine,[87] and the fractionation of serine, phenylalanine and methionine was achieved by the combined action of serine decarboxylase and phenylalanine ammonia-lyase (section 4.2.2.1).[88]

4.2.1.2 Chemocatalytic decarboxylation

Besides enzymes also common carbonyl compounds such as benzaldehyde, acetophenone and derivatives thereof are able to facilitate the non-oxidative decarboxylation of amino acids to primary (or secondary) amines. These aldehydes and ketones interact with the amino acid to generate a Schiff base adduct (Scheme 7), thereby mimicking the mode of operation of pyridoxal 5'-phosphate and the pyruvoyl cofactor in amino acid decarboxylases. Whereas the enzymatic reactions typically proceed in aqueous media under very mild conditions, chemocatalytic decarboxylation is generally performed at higher temperatures (*e.g.* 120-270 °C), hence in high-boiling and often toxic organic solvents such as nitrobenzene,[179] *N*,*N*-dimethylformamide,[180] hexamethyl phosphoramide[180] or cyclohexanol.[181] Water has an adverse effect on the Schiff base equilibrium and should therefore be avoided in the process medium. According to the mechanism the carbonyl compound is not consumed and thus should act as an organocatalyst (Scheme 7). However, the decarboxylation is typically carried out with a large molar excess of carbonyl compound to produce the desired amine in sufficient yield within relatively short reaction times; the reaction can even be run under solvent-free conditions.[182,183] Unfortunately, besides amines also aldehydes were obtained as a result of transamination. The product selectivity is partially determined by the carbonyl compound, because the protonation of the azomethine ylide intermediate can occur on either the α-carbon (preferred) or the γ-position as a result of 1,3-prototropy (Scheme 7, step **C**).[184] Transamination is more pronounced when using aromatic aldehydes and ketones with an electron-withdrawing substituent on the *ortho*- or *para*-position of the ring, because the negative charge of the carbanion will be located mainly on the γ-carbon. On the other hand, aromatic carbonyl compounds with electron-donating substituents keep the negative charge located on the α-carbon center, and reduce the tendency towards transamination.[179,180,182,185,186] De Vos and coworkers evaluated various types of carbonyl compounds in the decarboxylation of phenylalanine and elucidated that the reaction rate is strongly determined by the molecular structure of both the catalyst and the substrate. α,β-Unsaturated ketones and in particular isophorone were identified as performant organocatalysts in 2-propanol at 150 °C, *e.g.* 15 amino acids were converted to the corresponding amines in 28-99% yield after 24 h by using only 5 mol% isophorone.[187]

Peroxides such as tetralin hydroperoxide have also been suggested as catalysts for amino acid decarboxylation. For instance, isopentylamine was obtained in 10-95% yield by performing the decarboxylation of leucine with small amounts of peroxides (0.5-2 mol%) in an inert hydrocarbon solvent at 160-190 °C for 4-8 h.[188] Solvent selection appeared to be an important aspect, with higher amine yields in cyclic, aromatic hydrocarbons (*e.g.* tetralin) than in aliphatic hydrocarbons (*e.g.* squalane). However, tetralin hydroperoxide decomposes easily to 1-tetralone at elevated temperatures (> 130 °C),[189] and therefore the decarboxylation was most probably facilitated by this α,β-unsaturated aromatic ketone rather than by the peroxide itself.

Another metal-free, organocatalytic strategy for the non-oxidative decarboxylation of amino acids has been developed by



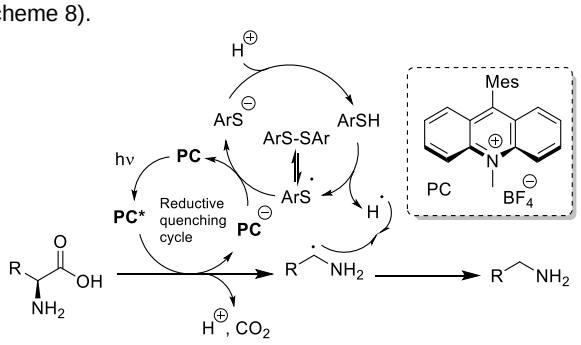
Scheme 7. Mechanism for the organocatalytic decarboxylation of an α-amino acid (**I**): (**A**) condensation of **I** with the carbonyl compound (**II**), (**B**) decarboxylation of the Schiff base adduct (**III**), (**C**) protonation of the azomethine ylide intermediate (**IV**), and (**D**) hydrolysis of the Schiff base adduct (**V**), with release of an amine (**VI**) and regeneration of the catalyst. Transamination, where **II** is consumed and **I** is converted to the corresponding aldehyde (**VII**), can be a competitive side reaction.[187]

Eventual beneficial solvent effects on the rate of decarboxylation should be interpreted carefully, because the activity of certain carbonyl compounds might have been overestimated by the presence of α,β-unsaturated ketone impurities, *e.g.* 1-tetralone in tetralin,[188] or 2-cyclohexen-1-one in cyclohexanol.[181]

Organocatalytic decarboxylation proceeds successfully for amino acids with an aliphatic or aromatic side chain. However, modification of pH-dependent functional groups in other amino acids is recommended to maintain high catalytic activity. For instance, glutamic acid is converted easily to pyroglutamic acid under these conditions and this derivative does not contain an accessible handle for Schiff base formation anymore. The decarboxylation of lysine to cadaverine was also challenging because both the α- and ε-amino group are in competition for Schiff base formation with the organocatalyst. Nevertheless, amino acid-derived amines have various applications, ranging from potential bulk chemicals like cadaverine and other alkylamines to fine chemicals such as tyramine and tryptamine. Moreover, the retention of chiral centers in the side chain of particular amino acids is advantageous regarding the synthesis of pharmaceuticals. For instance, (*R*)-3-hydroxypyrrolidine derived from (*R*)-4-hydroxyproline[190] is a precursor to alkaloids and detoxine A1,[191] whereas tryptamine derived from tryptophan[192,193] can be modified to psycho-active compounds such as *N*,*N*-dimethyltryptamine[194] and *N*,*N*-dimethylserotonine.[195] When the decarboxylation of amino acids is performed in *N*,*N*-dimethylformamide, N-formylation of the primary amines is observed as well, resulting in a one-pot process for the synthesis of amino acid-derived formamides, which are in turn direct precursors to isocyanides.[187] Application of the organocatalytic decarboxylation method to aqueous amino acid streams remains however an important challenge. To that end, the reaction can be performed in a high-boiling solvent such as dibenzyl toluene or isononanol, which allows continuous azeotropic removal of water. The amines can be isolated by evaporation, thereby using CO_2 as a stripping gas. In this way, cadaverine was obtained in 23-48% yield from lysine.[196]

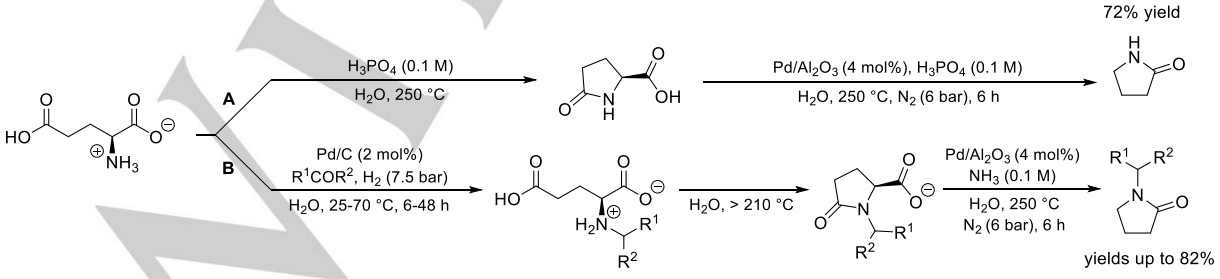
Wallentin and coworkers. A system consisting of 9-mesityl-10-methylacridinium tetrafluoroborate as a photoredox catalyst in

combination with bis(4-chlorophenyl)disulfide as a redox-coupled hydrogen shuttle was able to convert 21 amino acids at room temperature under visible light irradiation in 51-99% yield.[197] However, the reaction proceeds in hazardous dichloroethane and a protecting group on the amine moiety at the α-carbon and eventually in the side chain was again required to maintain a high selectivity, especially in the presence of free-radical species (Scheme 8).



Scheme 8. Mechanism for the photocatalytic decarboxylation of amino acids.[197] PC: photocatalyst; PG: protecting group; DDDS: bis(4-chlorophenyl)disulfide.

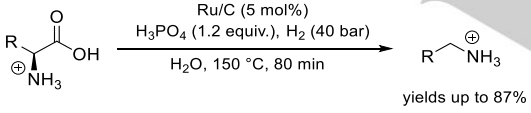
The non-oxidative decarboxylation of amino acids can also be mediated by transition metal catalysis. On the one hand, Djakovitch and coworkers reported on a Cu^{I}-1,10-phenanthroline (1:1) complex, prepared *in situ* by reduction of $Cu(OH)_2$, which catalyzed the decarboxylation of phenylalanine and tyrosine in polyethylene glycol at 210 °C; the corresponding amines were isolated in 68% yield.[198] However, the general applicability is limited, because the amines derived from aliphatic amino acids were only obtained in very low yield and other compounds even decomposed under these harsh conditions. Moreover, the method required high metal and ligand loadings (10 mol%) and the presence of water was found to be detrimental in terms of catalyst activity and stability. On the other hand, De Vos and coworkers found that Pd/Al_2O_3 is an effective heterogeneous catalyst for the decarboxylation of pyroglutamic acid to 2-pyrrolidone in aqueous media at 250 °C under inert atmosphere (Scheme 9, route **A**).[199] Besides pyroglutamic acid also glutamic acid can be used as a starting material since the latter is readily converted to its lactam derivative at 250 °C; for instance, 2-pyrrolidone was obtained in 72% yield at 92% conversion after 6 h in a one-pot process starting from glutamic acid. This drop-in route towards 2-pyrrolidone provides an alternative to the two-step, bio-based enzymatic or fermentative synthesis starting from glutamic acid (section 4.2.1.1) and the petroleum-based industrial production from γ-butyrolactone and NH_3.[200] 2-Pyrrolidone and derivatives thereof (*e.g.* *N*-vinyl-2-pyrrolidone and *N*-methyl-2-pyrrolidone) are widely applied as high-boiling solvents, polymer precursors (*e.g.* for nylon-4 or polyvinylpyrrolidone), surfactants, pharmaceuticals and agrochemicals.[201,202] Interestingly, a range of C_3-C_5 *N*-alkyl-2-pyrrolidones (*e.g.* *N*-butyl-2-pyrrolidone) has recently been proposed as sustainable alternatives for commonly used toxic solvents such as *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAc);[203] the latter solvents are categorized as 'Substances of Very High Concern for Authorization' by REACH and their use should be abandoned in the chemical industry.[204] In this context, De Vos and coworkers extended their work to the production of *N*-alkyl-2-pyrrolidones from glutamic acid *via* a three-step method which can be performed in aqueous media: (i) Pd-catalyzed reductive N-alkylation of glutamic acid with C_3-C_5 ketones and aldehydes; (ii) thermal cyclization to *N*-alkylpyroglutamic acid; and (iii) Pd-catalyzed decarboxylation to *N*-alkyl-2-pyrrolidone (Scheme 9, route **B**).[205] The first step is catalyzed by Pd/C under very mild conditions (*e.g.* 2 mol% Pd, 2-6 equiv. aldehyde or ketone, 25-70 °C, 7.5 bar H_2, 6-48 h) in order to obtain the mono-alkylated product in > 85% yield. Although both glutamic acid and monosodium glutamate can be used as raw materials, the N-alkylated derivatives of pyroglutamic acid should be purified from inorganic salts, because these were detrimental for the catalytic activity in the decarboxylation step. By applying similar conditions as for the decarboxylation of pyroglutamic acid (*e.g.* 4 mol% Pd, 6 bar N_2, 250 °C, 6 h), *N*-alkyl-2-pyrrolidones were obtained in 57-66% yield at near-complete conversion. Neutralization of *N*-alkylpyroglutamic acid by NH_3 appeared to slow down the undesired hydrolysis of the lactam moiety and further degradation reactions, which is beneficial in terms of selectivity; in this way yields up to 82% were realized. Moreover, *N*-alkyl-2-pyrrolidones can even be produced *via* a one-pot process mediated by Pd/Al_2O_3; the reactions proceed in a consecutive fashion by simply changing the gas atmosphere and temperature. However, product purification will not be straightforward,



Scheme 9. Transformation of glutamic acid to 2-pyrrolidone and derivatives thereof: intramolecular condensation to pyroglutamic acid, followed by Pd-catalyzed decarboxylation to 2-pyrrolidone (route **A**);[199] Pd-catalyzed reductive N-alkylation with carbonyl compounds, intramolecular condensation to *N*-alkylpyroglutamic acid and Pd-catalyzed decarboxylation to *N*-alkyl-2-pyrrolidone (route **B**).[205]

since *N*-alkyl-2-pyrrolidones are high-boiling compounds and evaporation of water is energetically demanding. Besides, the scope of this Pd-catalyzed decarboxylation process is somehow limited to glutamic acid because the functional groups present in other amino acids - in particular alcohols and amines - will be affected at 250 °C. A slightly adapted catalytic system has been developed for the decarboxylation of proline. Pyrrolidine was obtained in 69% yield after 2 h by using a Pb-modified Pd/ZrO_2 catalyst (4 mol% Pd) at 235 °C under 4 bar H_2.[206] Doping of the noble metal catalyst with Pb appeared to be an effective measure to increase the selectivity towards the secondary amine.

A more widely applicable, indirect decarboxylation approach involves the hydrogenation-decarbonylation or reductive deoxygenation of amino acids to primary (or secondary) amines.[207] The reaction is facilitated by Ru/C and proceeds under conditions that favor amino acid hydrogenation, *viz.* an aqueous medium at low pH and high H_2 pressures (section 4.1.1), but here C-C bond cleavage is achieved by raising the temperature to 150 °C (Scheme 10). The aliphatic amino acids valine, leucine and isoleucine were converted to the corresponding amines in 76-87% yield. Moreover, the products obtained from different amino acids were convergent in some cases, *e.g.* ethylamine was formed from glycine, alanine, serine, asparagine and aspartic acid. In this way, a mixture of amino acids can be converted to a limited group of short aliphatic primary amines, amongst others methylamine, ethylamine, *n*-propylamine, isopropylamine *etc*. These alkylamines are highly interesting industrial building blocks and could afford an added value for the neutral amino acid fraction recovered from protein waste. However, the S-containing amino acids cysteine and methionine act as catalyst poisons and should be removed in advance. Nevertheless, this method is characterized by a rather low atom efficiency due to the loss of multiple functional groups and carbon atoms.



Scheme 10. Ru-catalyzed hydrogenation-decarbonylation of amino acids to primary amines.[207]

4.2.1.3 Oxidative decarboxylation

The oxidative decarboxylation of amino acids to nitriles is generally mediated by hypohalite species, which can be produced from organic oxidants such as *N*-bromosuccinimide,[208,209] chloramine-T[210,211] and trichloroisocyanuric acid (Figure 6, **I**-**III**).[212,213] Sodium hypobromite can be also used as well, but this oxidant is rather unstable and hence more difficult to handle.[214,215] The oxidative decarboxylation proceeds often at room temperature in organic solvents, except when hypervalent iodine(V) oxidants such as *o*-iodoxybenzoic acid and Dess-Martin periodinane (Figure 6, **IV** and **V**) are involved, because they are known to facilitate the reaction in aqueous NH_3 at slightly higher temperature (*e.g.* 75 °C).[216]

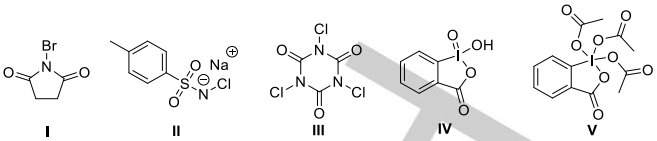


Figure 6. Hypohalite-containing oxidants that have been used for the oxidative decarboxylation of amino acids to nitriles: *N*-bromosuccinimide (**I**), chloramine-T (**II**), trichloroisocyanuric acid (**III**), *o*-iodoxybenzoic acid (**IV**) and Dess-Martin periodinane (**V**).

The substantial organic waste load (*viz.* co-products and solvents) associated with these state-of-the-art methods was a strong incentive to explore strategies that combine the oxidative decarboxylation of amino acids with *in situ* (re)generation of the oxidant, *viz.* hypobromite. Although sodium hypochlorite is a suitable oxidant for that purpose, it generates stoichiometric amounts of sodium chloride waste and is often used in large excess. The process medium should also be cooled to counteract the exothermic nature of bromide oxidation with hypochlorite.[217] Moreover, this method has only been reported for the transformation of glutamic acid to 3-cyanopropanoic acid, which was obtained in 70% yield. Continuous regeneration of hypobromite without generating inorganic waste has been achieved by electrocatalytic oxidation of a bromide salt.[218,219] De Vos and coworkers designed an electrochemical cell consisting of a Pt anode and a Ni cathode, where sodium bromide acts both as an electrolyte and as a precursor to the hypobromite. In this way a broad range of amino acids was converted to the corresponding nitriles in 77-94% yield (18 examples).[220] Alternatively, haloperoxidases can facilitate the oxidative decarboxylation of amino acids. These enzymes do not directly interact with the amino acid, but catalyze the generation of hypobromite species from sodium bromide by using H_2O_2 as a terminal oxidant, thereby producing water as the only co-product. They operate in a buffered aqueous medium (pH 5-7) and require only catalytic amounts of sodium bromide.[221–224] However, although the reaction proceeds with excellent nitrile selectivity for acidic amino acids, competitive aldehyde formation (up to 25% at full conversion) was observed for neutral amino acids such as valine and phenylalanine.

The selectivity towards nitriles has been improved by developing another catalytic system, where immobilized (peroxo)tungstate species were applied as a catalyst for halide oxidation, again using H_2O_2 as the terminal oxidant.[93] The acid-base properties of the system were carefully balanced by selecting the slightly acidic ammonium bromide salt in combination with a mildly basic takovite-type support. Moreover, H_2O_2 was supplied continuously during the reaction to avoid unproductive singlet oxygen ($^1O_2$) generation and to increase the oxidant efficiency. The system has been applied successfully for the majority of the amino acids (14 examples), *e.g.* nitrile yields up to 99% were obtained starting from monosodium glutamate or leucine, and even 5-aminopentanenitrile was obtained in 90% from lysine. Moreover, the robustness of the system was demonstrated in a case study on hydrolyzed wheat gluten, where the catalytic performance could be maintained in the presence of

other residual biomass constituents. The potential to tackle real waste streams of higher complexity is very promising regarding industrial applications.

Although the oxidative decarboxylation of amino acids has already been improved in terms of *green chemistry*, the reaction could not be performed in the absence of halides until the advent of a metal-catalyzed strategy. Inspired by the aerobic oxidation of primary amines to nitriles, De Vos and coworkers found that $Ru(OH)_x/Al_2O_3$ was an effective catalyst for the oxidative decarboxylation of amino acids in water at 100 °C.[225] In contrast to the previous methods, the amino acid interacts directly with the metal catalyst and for the first time molecular oxygen (O_2) has been applied as a terminal oxidant for this reaction. The substrate scope is limited to amino acids with an aliphatic or acidic side chain from which the corresponding nitriles were obtained in 70-80% yield (7 examples), but there is still room for improvement, in particular regarding functionalized amino acids.

Among the abovementioned methods for oxidative decarboxylation of amino acids, the ones based on hypobromite have the largest substrate scope. Nevertheless, oxidative ring bromination in amino acids with a phenolic or hetero-aromatic moiety, *viz.* tyrosine, tryptophan and histidine, is considered as a common disadvantage. Therefore, this method is particularly interesting for upgrading the acidic amino acid fraction consisting of glutamic acid and aspartic acid.[223] For instance, the oxidation product of glutamic acid, *viz.* 3-cyanopropanoic acid, is an intermediate towards other industrially relevant nitriles such as acrylonitrile, succinonitrile and adiponitrile; catalytic pathways towards each of these products have been reported (Scheme 11). On the one hand, homocoupling of 3-cyanopropanoic acid to adiponitrile proceeds with > 75% yield by the Kolbe reaction using Pt electrodes; the overall yield based on glutamic acid was 58% (route **A**).[219] On the other hand, succinonitrile was produced in 62% yield by Pd-catalyzed dehydration of 3-cyanopropanoic acid (route **B**),[226] whereas acrylonitrile was obtained by Pd-catalyzed decarbonylation-elimination, albeit in low yield (route **C**).[217]

The previous examples on amino acid decarboxylation illustrate that glutamic acid can be recycled to a broad range of useful N-containing commodity chemicals. Moreover, they provide a bio-based alternative to conventional petrochemical processes, which are nowadays based on the incorporation of toxic NH_3 or HCN into olefins. However, the transformation of glutamic acid to nitriles is not yet attractive in terms of atom economy: the majority of the hetero-atoms and also a substantial fraction of the carbon mass are not retained in the end products. Moreover, a life cycle assessment for the production of acrylonitrile and succinonitrile from either glutamic acid or petrochemicals has demonstrated that the bio-based routes have a higher environmental impact than the conventional ones, because of the waste associated with the use of sodium hypochlorite as oxidant and the need for cooling the reaction mixture.[227] Nevertheless, it was assumed that the impact of the bio-based process would be substantially reduced by performing the reaction with oxygen at elevated temperature. In that respect the Ru-based method for oxidative decarboxylation of amino acids provides already good perspectives.

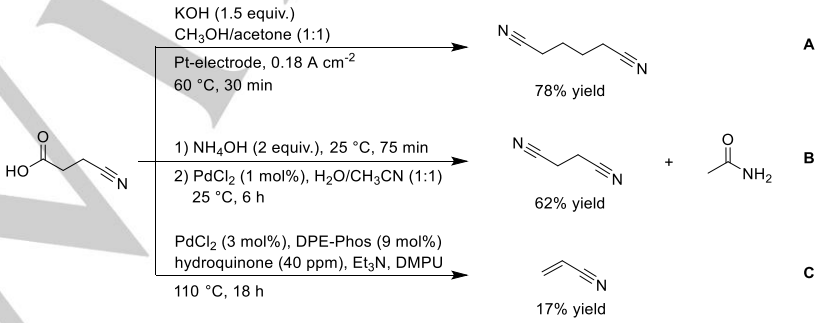
The oxidation of amino acids to nitriles seems especially useful in upgrading waste protein hydrolysates, because the separation of non-functionalized aliphatic and aromatic nitriles is at least more straightforward. Nitriles can be isolated with high purity from other residual biomass constituents by distillation or extraction. These valuable platform molecules are readily transformed into amines, amides and carboxylic acids.

4.2.2 Deamination of amino acids

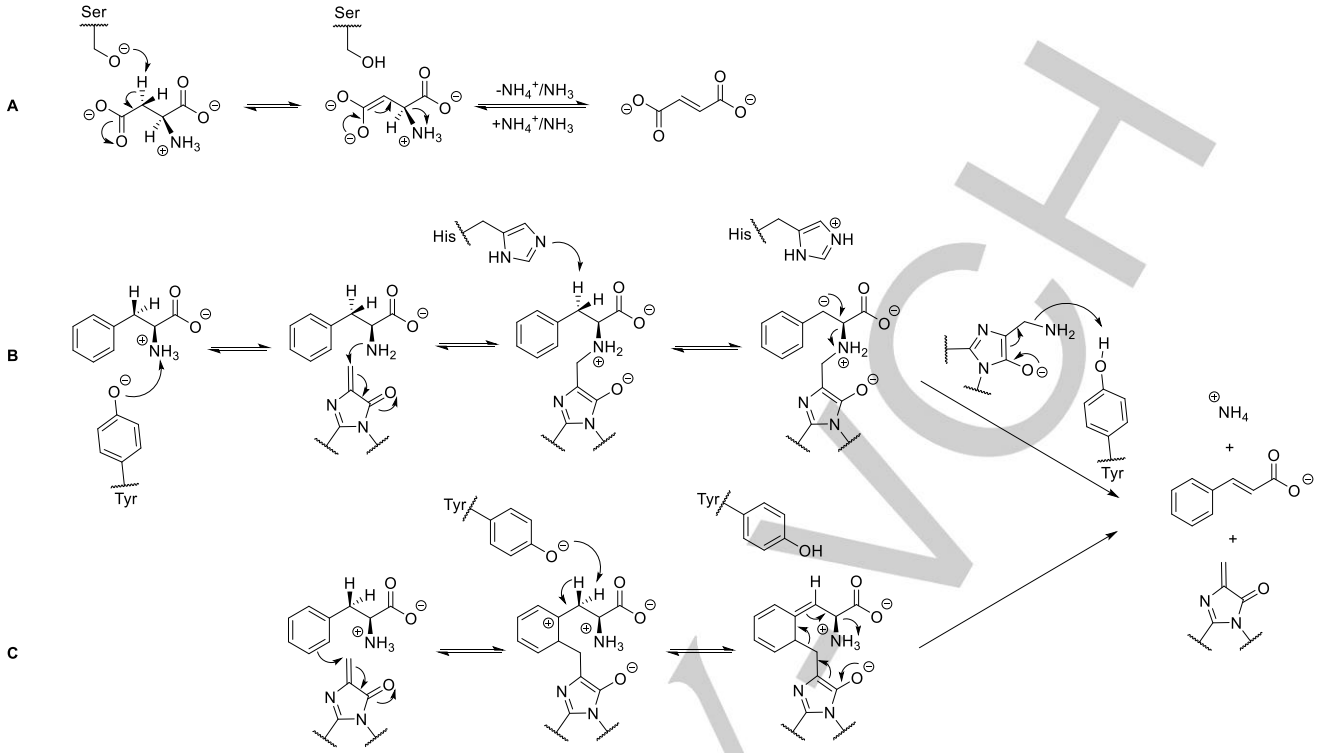
The deamination of amino acids is another interesting strategy in the valorization of protein-rich biomass to chemicals. Although this reaction involves the elimination of nitrogen and the majority of the natural amino acids are converted into relatively simple carboxylic acids, deamination of selected compounds provides access to value-added chemicals such as α,ω-bifunctional polymer precursors and α,β-unsaturated carboxylic acids. Enzymatic, chemical and chemocatalytic approaches for deamination will be discussed.

4.2.2.1 Enzymatic deamination

Ammonia-lyases catalyze the deamination of certain amino acids to α,β-unsaturated carboxylic acids, *e.g.* phenylalanine to cinnamic acid,[88] tyrosine to *p*-coumaric acid, and aspartic acid to fumaric acid.[228] However, the number of these enzymes is rather limited and they are characterized by a very high substrate specificity.[229] Although these ammonia-lyases operate through distinct mechanisms, abstraction of a proton at the β-position in the substrate followed by the elimination of NH_3 are common steps. In L-aspartate ammonia-lyase, on the one hand, the carbanion generated upon abstraction of a β-proton is stabilized by the formation of an enolate intermediate (Scheme 12, route **A**).



Scheme 11. Transformation of 3-cyanopropanoic acid to adiponitrile (route **A**),[219] succinonitrile (route **B**)[226] and acrylonitrile (route **C**).[217] DPE-Phos: bis-[2-(diphenylphosphino)phenyl]ether; DMPU: 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one.

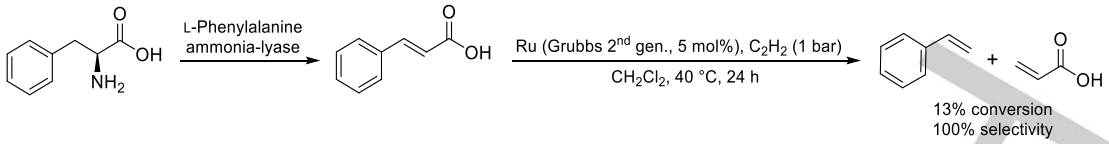


Scheme 12. Enzymatic deamination catalyzed by L-aspartate ammonia-lyase (route **A**) and L-phenylalanine ammonia-lyase *via* a MIO-mediated E1cB elimination mechanism (route **B**) or a Friedel-Crafts-type mechanism (route **C**).[229,230]

The substrate specificity can be attributed to specific hydrogen bond interactions between the enzyme and the carboxylate groups of the substrate and also to the generation of a product with a conjugated electronic system (*viz.* fumarate).[229] In aromatic amino acid ammonia-lyases, on the other hand, the substrate is activated by the 4-methylideneimidazol-5-one (MIO) cofactor. The exact mechanism is still under discussion but two modes of operation have been proposed for L-phenylalanine ammonia-lyase. The MIO cofactor performs an electrophilic attack either on the amine moiety followed by a E1cB mechanism (route **B**), or on the aromatic ring *via* a Friedel-Crafts-type mechanism (route **C**). In both cases the MIO cofactor is regenerated in the end.[229,230]

α,β-Unsaturated carboxylic acids have important applications in the chemical industry. For instance, cinnamic acid is a precursor to flavor-active compounds and pharmaceuticals but its main use is situated in the manufacturing of the corresponding alkyl or benzyl esters for the development of fragrances.[231] *p*-Coumaric acid is widely used in chemical, food, health, cosmetic and pharmaceutical industries. Over the past two decades it gained a lot of interest because of its anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties.[232] Fumaric acid is mostly applied in the formulation of food and beverages, in the paper industry and in the synthesis of unsaturated polyesters and alkyd resins. Somehow contradictory, these α,β-unsaturated carboxylic acids nowadays often serve as reagents in the synthesis of the corresponding amino acids (*e.g.* aspartic acid from fumaric acid, section 2.1).[228] Nevertheless, it is still conceivable that the increasing production of protein-rich biomass waste could result in large quantities of inexpensive amino acids, hence the enzymatic deamination of aspartic acid may become a cost-efficient method for the manufacturing of fumaric acid (currently about 900 € ton^{-1}).[233]

The decarboxylation of cinnamic acid and *p*-coumaric acid provides a bio-based route towards styrene and derivatives thereof. For example, recombinant L-phenylalanine over-producing *E. coli* strains that contain a.o. L-phenylalanine ammonia-lyase and *trans*-cinnamic acid decarboxylase are able to convert glucose directly to styrene, but the yield is mainly limited by the cytotoxicity of the olefin.[234] Alternatively, *p*-hydroxystyrene can be obtained in 63% yield by base-catalyzed decarboxylation of *p*-coumaric acid in DMF; microwave heating allows to reduce the reaction time to a few minutes. However, the scope is limited to *p*-coumaric acid and derivatives thereof, because the decarboxylation proceeds through a quinomethine intermediate.[235] Scott and coworkers proposed a highly atom-efficient strategy for the combined production of bio-styrene and bio-acrylates from phenylalanine using ethenolysis as a sequel to enzymatic deamination (Scheme 13). The metathesis reaction between cinnamic acid and ethylene was facilitated by a Hoveyda-Grubbs 2nd generation Ru catalyst under very mild conditions (*e.g.* 1 bar ethylene, 40 °C). Although the reaction proceeds with excellent selectivity, the conversion of cinnamic acid was very low (*viz.* 13%), even when the corresponding alkyl esters were used (*e.g.* up to 38% for *n*-butyl cinnamate) due to the presence of an electron-deficient unsaturated C-C bond in the



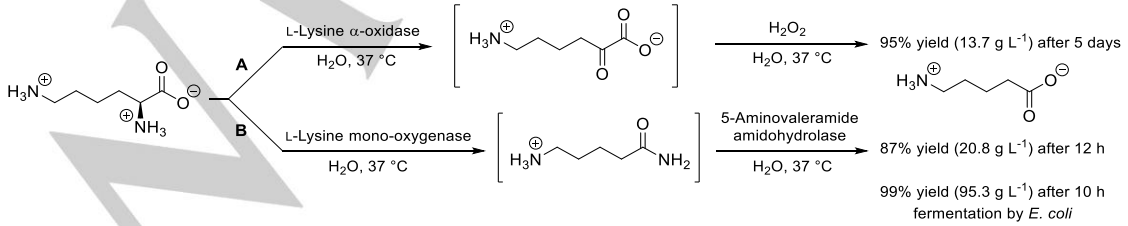
Scheme 13. Enzymatic deamination of L-phenylalanine to *trans*-cinnamic acid, followed by Ru-catalyzed ethenolysis to styrene and acrylic acid.[236]

substrate. Moreover, the reaction was performed in a halogenated solvent, which is not attractive for upgrading biomass in terms of *green chemistry*.[236]

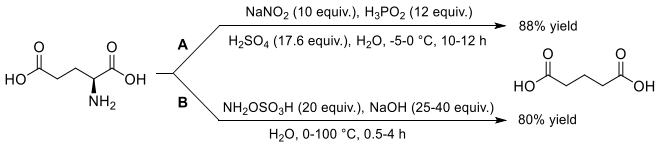
The elimination of NH_3 was also observed during the enzymatic oxidation of amino acids to α-keto acids. For instance, lysine α-oxidase transforms lysine to 6-amino-2-ketocaproic acid, NH_3 and an equimolar amount of H_2O_2. In cellular conditions, the latter is decomposed to water and O_2 by catalase and the intramolecular condensation of 6-amino-2-ketocaproic acid to Δ^1-piperidine-2-carboxylate proceeds spontaneously. However, in the absence of catalase, oxidative decarboxylation of 6-amino-2-ketocaproic acid with H_2O_2 produces 5-aminovaleric acid (Scheme 14, route **A**). This ω-amino acid is a precursor to δ-valerolactam, which is in turn the monomer of nylon-5. Franssen and coworkers developed an enzymatic, buffer-free system to convert a mixture of L-lysine and its hydrochloride salt to 5-aminovaleric acid with 95% yield at 13.7 g L^{-1} after incubation at 37 °C for 5 days. Moreover, lysine α-oxidase was successfully immobilized on an epoxy-activated solid support (*e.g.* Sepabeads EC-EP) to facilitate product isolation and enzyme recycling.[237] Alternatively, 5-aminovaleric acid can be produced in 99% yield at 95.3 g L^{-1} after 10 h in a fermentation process using a recombinant *E. coli* strain. This approach utilizes the 5-aminovalerate metabolic pathway where the enzymes L-lysine mono-oxygenase and 5-aminovaleramide amidohydrolase play key roles, respectively for converting lysine to 5-aminovaleramide and further to 5-aminovaleric acid.[238,239] Besides, both enzymes can be purified and used in a two-enzyme coupled reaction to produce 5-aminovaleric acid in 87% yield at 20.8 g L^{-1} after incubation at 37 °C for 12 h (Scheme 14, route **B**). Although the product concentrations are much lower compared to the fermentative approach, the composition of the process medium is less complex, which alleviates product work-up.[240] Recently, a recombinant *C. glutamicum* strain was developed to convert 5-aminovaleric acid further to glutarate,[241] another interesting bio-based building block (section 4.2.2.2).

4.2.2.2 Chemical deamination

The direct deamination of glutamic acid to glutaric acid is not facilitated by enzymes, but is particularly interesting because this C_5 diacid can be used either as a precursor for linear diols and diamines, or as a monomer in the synthesis of C_5 polyesters and polyamides. Glutaric acid is highly complementary to succinic acid and adipic acid due to its distinct physicochemical properties attributed to the odd carbon number, thereby providing access to specialty polymers. The industrial production of the C_4 and C_6 linear diacids is well-established, whereas glutaric acid is nowadays only available as a minor by-product (2%) from adipic acid synthesis - the current market volume of this commodity chemical exceeds 2.5 million tons per year[242,243] - but is gaining attention.[244] Recently, a bio-based route towards glutaric acid has been developed and involves the catalytic oxidation of pentose sugars to pentaric acid using Pt/SiO_2, followed by catalytic hydrodeoxygenation using Rh/SiO_2. The yield of glutaric acid was, however, rather low (< 45%) and hydrohalic acids were required to speed up the reaction.[245] Chemical methods for deamination of amino acids may therefore be more appropriate. In one method the amine moiety in the amino acid is converted first into a diazonium salt, from which gaseous nitrogen (N_2) can be eliminated in the presence of a reducing agent.[246–248] For instance, glutaric acid was obtained in 88% yield upon treating glutamic acid in a highly acidic aqueous medium with an excess of sodium nitrite and hypophosphoric acid (Scheme 15, route **A**).[248] A second method involves the modification of the amino group in the substrate to a hydrazine by hydroxylamine-*O*-sulfonic acid under basic conditions (Scheme 15, route **B**). The hydrazine is then oxidized by a reactive nitrene intermediate - also generated from hydroxylamine-*O*-sulfonic acid under basic conditions - to a diazene (or diimide), which easily releases N_2 in the end.[249–252] In this way, glutaric acid and succinic acid were obtained from glutamic acid and aspartic acid in 80% and 90% yield, respectively.[251,252] These methods for chemical deamination can also be applied in the valorization of basic amino



Scheme 14. Transformation of L-lysine to 5-aminovaleric acid either by L-lysine α-oxidase in the presence of H_2O_2 (route **A**),[237] or by a combination of L-lysine mono-oxygenase and 5-aminovaleramide amidohydrolase (route **B**).[238–240]



Scheme 15. Direct deamination of glutamic acid to glutaric acid using $NaNO_2$ and H_3PO_2 in acidic media (route **A**)[246–248] or hydroxylamine-*O*-sulfonic acid (NH_2OSO_3H) in basic media (route **B**).[250–252]

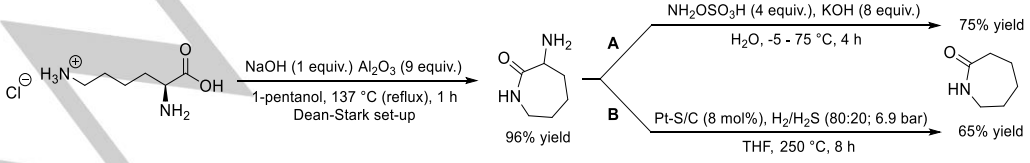
acids, in particular to obtain ε-caprolactam from lysine. Frost reported on a two-step process for that purpose, which involves the intramolecular condensation of lysine, followed by the deamination of α-amino-ε-caprolactam (Scheme 16, route **A**). The first step proceeds by heating the amino acid in an alcoholic solvent in the presence of Al_2O_3, combined with the withdrawal of water in a Dean-Stark trap. Subsequent deamination of α-amino-ε-caprolactam with hydroxylamine-*O*-sulfonic acid under basic conditions delivered ε-caprolactam in 75% yield.[253]

Despite their effectiveness, both chemical methods use an excess of reagents, generate large amounts of waste and release N_2 as an inert co-product. Methods that allow to recycle nitrogen in a more valuable co-product would be more appropriate, because nitrogen fixation in the chemical industry still relies on the energy-intensive Haber-Bosch process for NH_3 production.[16]

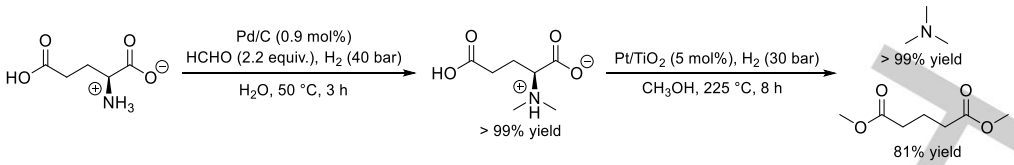
4.2.2.3 Chemocatalytic deamination

Chemocatalytic deamination of amino acids might reduce the waste load compared to the previous methods and eventually allows to recycle nitrogen as NH_3 or an organic nitrogenous compound. Several complementary Pt-based systems have been developed for the reductive deamination of acidic and basic amino acids under H_2 atmosphere. In the context of bio-based routes towards ε-caprolactam, Frost reported on the deamination of α-amino-ε-caprolactam using a sulfided Pt/C catalyst in tetrahydrofuran at 250 °C (Scheme 16, route **B**).[254,255] However, the system required both high metal and catalyst loadings (*e.g.* 16 wt% Pt/C, 8 mol% Pt) and the desired lactam was only obtained in 65% yield at full conversion, which is lower than in the chemical approach (Scheme 16, route **A**). The direct deamination of lysine hydrochloride with sulfided Pt/C (1 mol% Pt) in ethanol at 250 °C was even less successful, with only 15% yield of ε-caprolactam.[254,255] Moreover, the reaction was performed under a reducing atmosphere containing toxic H_2S (20 vol%) in order to facilitate the elimination of NH_3, though it is known that noble metal catalysts are easily deactivated by irreversible chemisorption of reduced sulfur species.[256] Very recently, De Vos and coworkers developed a two-step chemocatalytic process for the deamination of glutamic acid to dimethyl glutarate and trimethylamine.[92] In a first step glutamic acid is modified to *N*,*N*-dimethylglutamic acid by a mild Pd-catalyzed reductive *N*-alkylation in water using formaldehyde under H_2 atmosphere. Next, the deamination of the *N*-alkyl amino acid is performed in methanol at 225 °C under 30 bar H_2 but in the absence of H_2S. Pt/TiO_2 was demonstrated to be a powerful catalyst for this purpose, which can be attributed to a subtle interplay between the metal centers and the moderate acidity of the support: Lewis and Brønsted acid sites facilitate the adsorption of the substrate on the catalyst surface and activate the tertiary amine moiety, followed by Pt-catalyzed selective C-N hydrogenolysis. Low metal loadings (*e.g.* 1 wt% Pt/TiO_2, 5 mol% Pt) and hence a high dispersion were beneficial in terms of activity. Under these conditions glutaric acid and dimethylamine were readily converted to dimethyl glutarate and trimethylamine, with respective yields of 81% and > 99% after 8 h (Scheme 17). Moreover, this method provides a potential valorization path for the entire acidic amino acid fraction: when this catalytic system was applied to a mixture of glutamic acid and aspartic acid, dimethyl glutarate and dimethyl succinate were obtained in respectively 78% and 99% yield, together with trimethylamine. The resulting diester blends can be used as such for the synthesis of alkyd resins or as a *green* solvent, thereby avoiding expensive separation techniques such as distillation. Nevertheless, the separation of the corresponding diacids, *viz.* glutaric acid and succinic acid, would also be more straightforward compared to the amino acids due to a substantial difference in water solubility, respectively 639 g L^{-1} and 58 g L^{-1}. Besides, trimethylamine is a volatile co-product, which can be recovered easily from the process medium and can be used as a reagent in the manufacturing of vitamins, ion-exchange resins, solvents *etc.*[257]

The catalytic reductive deamination seems especially useful for upgrading the non-essential acidic amino acids. Aliphatic amino acids in the neutral fraction are mainly converted to non-functionalized carboxylic acids and amino acids with side chain functionalities such as alcohols and amines will probably be degraded at high temperature. Moreover, the economic feasibility for producing ε-caprolactam from lysine is nowadays rather poor, since the market volume of ε-caprolactam produced from cyclohexanone exceeds 4 million tons per year and this product is available at relatively low price (about 1,300 € ton^{-1}). However, the still increasing production of protein-rich biomass waste might result in lower amino acid prices, eventually making competition possible in the future. Besides, the simultaneous co-valorization of ornithine, which can be obtained by base-mediated or enzymatic hydrolysis of arginine,[8,148] to δ-valerolactam might be useful for upgrading the entire basic amino acid fraction and increase the economic feasibility. However, this route has not been explored yet.



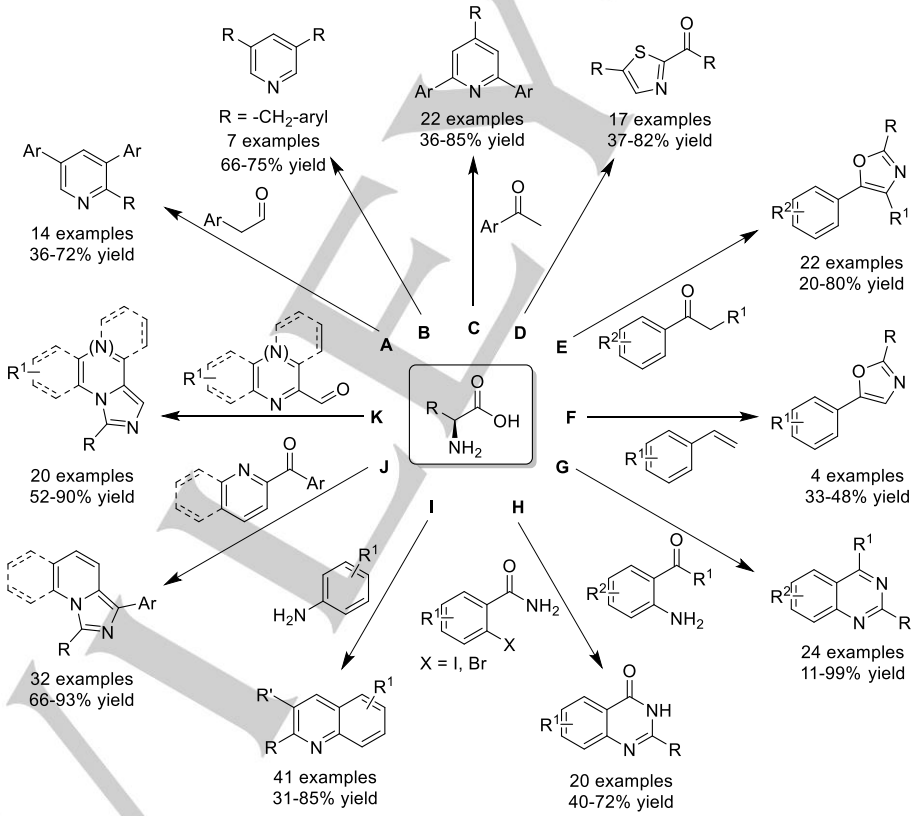
Scheme 16. Transformation of lysine to ε-caprolactam by intramolecular condensation to α-amino-ε-caprolactam, followed by chemical deamination using hydroxylamine-*O*-sulfonic acid (route **A**),[253] or by Pt-catalyzed reductive deamination (route **B**).[255]



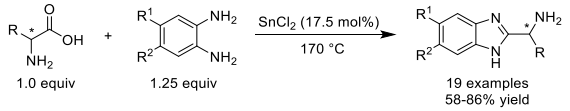
Scheme 17. Transformation of glutamic acid to dimethyl glutarate and trimethylamine by Pd-catalyzed reductive N-alkylation in water and Pt-catalyzed reductive deamination in methanol.[92]

5 Amino acids as versatile reagents in organic synthesis

Amino acids are interesting precursors to a range of N-heterocycles with potential bio-activity, which is attributed to the presence of characteristic amino acid side chain moieties. This approach provides opportunities for the development of pharmaceuticals, agrochemicals and other fine chemicals. Scheme 18 exemplifies several synthetic routes towards amino acid-derived pyridines (routes **A**-**C**),[258–260] thiazoles (route **D**),[261] oxazoles (routes **E** and **F**),[261–263] quinazolines (route **G**),[264] quinazolin-4(3*H*)-ones (route **H**),[265] quinolines (route **I**)[266] and imidazo[1,5-*a*]N-heterocycles (routes **J** and **K**).[267–269] Amino acid decarboxylation is a common step in these reactions and is typically facilitated by molecular iodine (I_2) and/or a homogeneous Cu catalyst; I_2 is involved in the oxidative decarboxylation of amino acids to imines. Whereas some methodologies have only been demonstrated for glycine and amino acids with a short aliphatic side chain, other procedures proved also to be successful for amino acids containing protected functional groups in the side chain. Amino acids have also been involved in the solvent-free synthesis of 2-aminomethyl-benzimidazoles, which proceeds by condensation with *o*-diaminobenzene and intramolecular cyclization in the presence of a Sn catalyst (Scheme 19).[270]

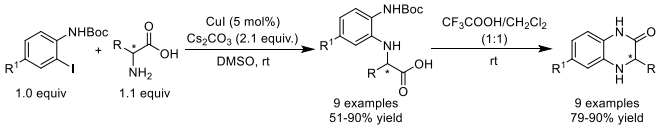


Scheme 18. Synthesis of amino acid-derived N-heterocycles. Conditions: (**A**) aryl acetaldehyde (1.25 equiv.), I_2 (0.3 equiv.), TBHP (1.25 equiv.), DMAc, 4Å MS, 70 °C, N_2;[258] (**B**) acetic acid (1.0 equiv.), I_2 (0.5 equiv.), DMSO, 115 °C;[259] (**C**) methyl aryl ketone (1.0 equiv.), I_2 (1.0 equiv.), pyridine, 120 °C;[259] (**D**) $Na_2S.9H_2O$ (0.6 equiv.), acetic acid (0.25 equiv.), I_2 (1.0 equiv.), DMSO, 100 °C;[261] (**E**) aryl methyl ketone (0.33 equiv.), I_2 (7 mol%), oxone (1.0 equiv.), DMSO, 95 °C;[263] (**F**) styrene (2.0 equiv.), I_2 (0.2 equiv.), acetic acid (3.0 equiv.), oxone (2.5 equiv.), DMSO, 95 °C;[263] (**G**) 2-aminobenzoketone (0.67 equiv.), I_2 (0.33 equiv.), TBHP (1.33 equiv.), DMAc, 80 °C;[264] (**H**) 2-halobenzamide (0.5 equiv.), CuBr (5 mol%), K_2CO_3 (1.5 equiv.), DMSO/ethylene glycol (75:1), air, 120 °C;[265] (**I**) 2nd amino acid (1.0 equiv.), aniline (1.0 equiv.), HI (0.5 equiv.), I_2 (1.0 equiv.), DMSO, 100 °C;[266] (**J**) 2-benzoylpyridine or 2-benzoylquinoline (0.33 equiv.), $Cu(OTf)_2$ (5 mol%), I_2 (5 mol%), di-*tert*-butyl peroxide (0.83 equiv.), toluene, 120 °C;[267] (**K**) N-heterocyclic carbaldehyde (0.91 equiv.), I_2 (0.91 equiv.), $KHCO_3$ (1.82 equiv.), DMAc, 4Å MS, 35 °C.[268] TBHP: *tert*-butyl hydroperoxide; MS: molecular sieves.



Scheme 19. Synthesis of 2-aminomethyl-benzimidazoles from amino acids.[270]

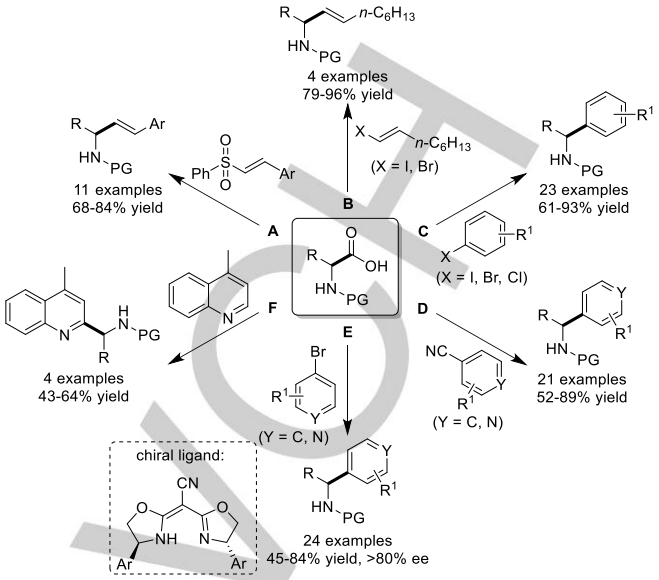
In addition, amino acids are useful reagents in cross-coupling reactions, as exemplified by the synthesis of quinazolin-4(3*H*)-ones (Scheme 18**Error! Reference source not found.**, route **G**)[265] or the synthesis of dihydroquinoxalinones derived from phenylalanine, valine and tryptophan (Scheme 20).[271] The latter two-step reaction involves a Cu-catalyzed N-arylation of the unprotected amino acid with *N*-Boc-2-iodoaniline, followed by acid-mediated Boc-deprotection and cyclization.



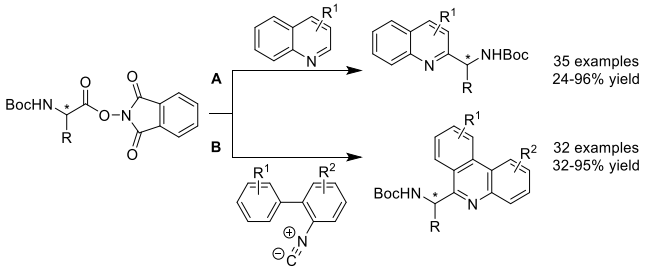
Scheme 20. Synthesis of amino acid-derived dihydroquinoxalinones.[271]

MacMillan and coworkers developed several complementary methodologies for the decarboxylative cross-coupling of *N*-Boc-protected amino acids (Scheme 21). In the presence of homogeneous Ir-based photoredox catalysts amino acids can be coupled with vinyl sulfones (route **A**),[272] vinyl halides (route **B**),[273] aryl halides (route **C**)[274] or aromatic nitriles (route **D**)[275] upon illumination with visible light to produce allylic and benzylic amines. Moreover, enantio-enriched benzylic amines can be obtained in the presence of chiral Ni catalysts (route **E**).[276] Glorius and coworkers applied these photoredox catalysts in the visible light-mediated decarboxylative C-H functionalization of hetero-arenes, thereby using ammonium persulfate ($(NH_4)_2S_2O_8$) as an oxidant. The protocol was demonstrated for the coupling of lepidine with a few *N*-acetyl-protected amino acids (route **F**).[277] Recently, amino acid esters have been applied as a coupling partner in the challenging direct C-H amination of phenols, aromatic ethers and non-functionalized arenes using an acridinium photoredox catalyst.[278] In addition, Li and coworkers reported on C_{sp3}-C_{sp2} and C_{sp3}-C_{sp} bond formation *via* the decarboxylative coupling of proline derivatives with hetero-aromatic compounds and alkynes in the presence of Fe-[279] or Cu-based catalysts.[280,281]

Redox-active phthalimide esters of *N*-Boc-protected amino acids have also been involved in the synthesis of N-heterocycles (Scheme 22). For instance, phenanthridines were obtained by coupling with 2-isocyanobiphenyls under visible light irradiation in the presence of ruthenium bipyridine, which acts as a photoredox catalyst (route **B**).[282] The protocol has been applied successfully to the majority of the natural amino acids. The mechanism involves a decarboxylation step, thereby generating an amino acid-derived free-radical intermediate; hence, protection of functional groups in the substrate was required to maintain a high selectivity.

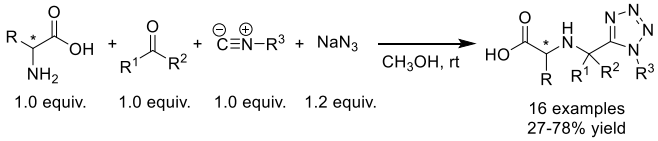


Scheme 21. Decarboxylative coupling of amino acids containing a protecting group (PG) on the amine moiety in the presence of Ir-based photoredox catalysts upon irradiation with visible light. Conditions: (**A**) vinyl sulfone (1.0 equiv.), *N*-Boc-amino acid (1.2 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.5 mol%), $CsHCO_3$ (2.0 equiv.), 1,4-dioxane, 50 °C, 26 W CFL;[272] (**B**) vinyl halide (1.0 equiv.), *N*-Boc-amino acid (1.6 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), $NiCl_2$.glyme (2 mol%), dtbbpy (2 mol%), DBU (1.6 equiv.), DMSO, rt, 34 W blue LED;[273] (**C**) aryl halide (1.0 equiv.), *N*-Boc-amino acid (3.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%), $NiCl_2$.glyme (10 mol%), dtbbpy (15 mol%), Cs_2CO_3 (3.0 equiv.), DMF, rt, 26 W CFL;[274] (**D**) aromatic nitrile (1.0 equiv.), *N*-Boc-amino acid (3.0 equiv.), Ir[*p*-F(*t*Bu)-ppy]$_3$ (2 mol%), CsF (3.0 equiv.), DMSO, rt, 26 W CFL;[275] (**E**) aryl bromide (1.0 equiv.), *N*-Boc-amino acid (1.5 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol%), $NiCl_2$.glyme (2 mol%), chiral ligand (2.2 mol%), Cs_2CO_3 (1.8 equiv.), tetrabutylammonium iodide (0.1 equiv.), dimethyl ether/toluene, rt, blue LED;[276] (**F**) lepidine (1.0 equiv.), *N*-acetyl-amino acid (10.0 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.5 mol%), $(NH_4)_2S_2O_8$ (2.0 equiv.), DMSO, rt, blue LED.[277] $[dF(CF_3)ppy]_2(dtbbpy)$: [4,4'-bis(*tert*-butyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; CFL: compact fluorescent lamp; LED: light emitting diode.



Scheme 22. Synthesis of N-heterocycles from *N*-hydroxyphthalimide esters derived from *N*-Boc-protected amino acids. Conditions: (**A**) hetero-arene (0.67 equiv.), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 mol%), (±)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (1 mol%), DMAc, Ar, rt, 36 W blue LED;[283] (**B**) 2-isocyanobiphenyl (0.33 equiv.), $[Ru(bpy)_3]Cl_2$ (0.33 mol%), *N*,*N*-diisopropylethylamine (0.13 equiv.), K_2CO_3 (0.4 equiv.), DMF, rt.[282] $[dF(CF_3)ppy]_2(dtbbpy)$: [4,4'-bis(*tert*-butyl)-2,2'-bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl].

In the previous examples the molecular structure of amino acids was only partially retained in the end product. The opposite was shown by Dömling and coworkers for the Ugi-tetrazole reaction, where amino acids were combined together with aldehydes, isocyanides and sodium azide (Scheme 23).[284] Furthermore, morpholine-substituted amino acids have been prepared by amidation of the carboxylic acid moiety using a carbodiimide coupling reagent in the presence of 1-hydroxybenzotriazole.[285] Again, Boc- or Cbz-protecting groups on the amine moiety are a prerequisite in terms of product selectivity.



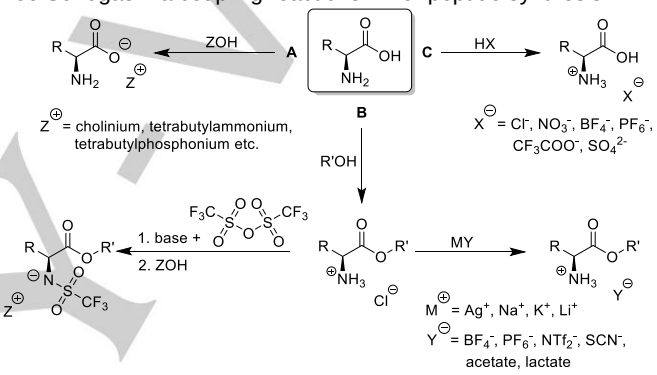
Scheme 23. Ugi-tetrazole multicomponent reaction.[284]

These examples clearly demonstrate how amino acids can find their way into the development of pharmaceuticals and other fine chemicals. Especially the neutral amino acid fraction has the highest potential for this purpose. Obviously the work-up of these process mixtures can be demanding but this is largely compensated by the added value of the end product.

6 Amino acids in the synthesis of ionic liquids

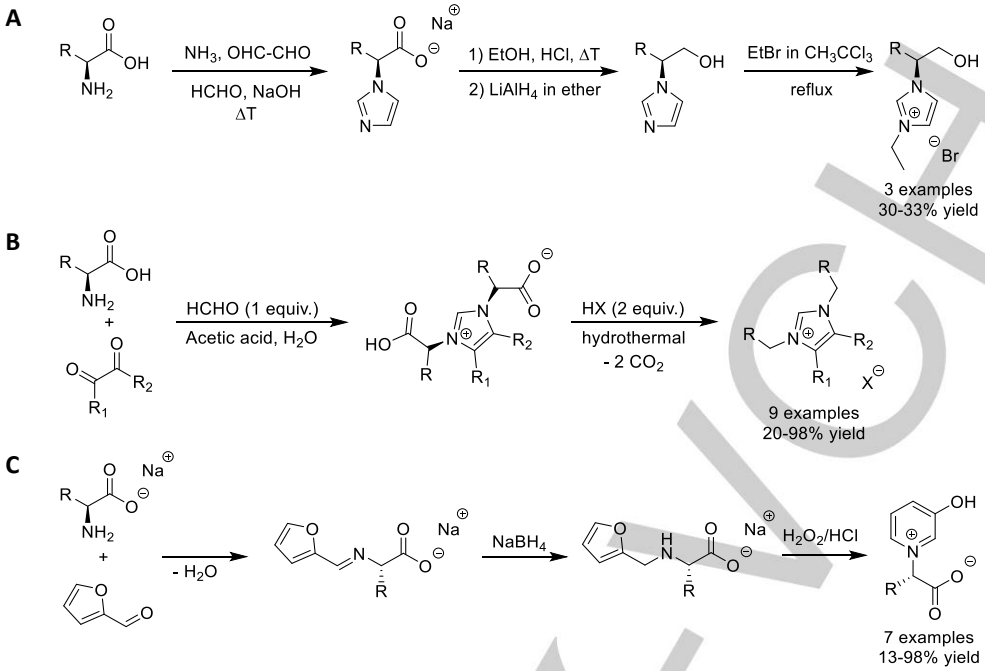
Amino acids and their derivatives have also been involved in the synthesis of bio-based ionic liquids,[286,287] thereby being highly complementary to the current portfolio of ionic liquids that are mainly composed of quaternary ammonium, imidazolium, pyridinium or phosphonium cations combined with halogenated anions such as Cl^-, PF_6^-, BF_4^-, $N(CF_3SO_2)_2^-$, $CF_3CO_2^-$ or $CF_3SO_3^-$. These low-melting salts (T_{mp} < 100 °C) are generally characterized by negligible volatility, non-flammability, high chemical and thermal stability, high ionic conductivity and low viscosity. In addition, amino acid-based ionic liquids may contain a chiral centre and are eventually biocompatible, biodegradable and of low toxicity.[288–291] The physical and chemical properties can be tuned by the type and composition of the cations and anions; ionic liquids are therefore considered as 'designer solvents'. The most important routes towards amino acid-based ionic liquids will be discussed briefly, thereby highlighting the potential applications. The molecular structure of the amino acid can be retained in the ionic liquid, or can be used as a scaffold for building common N-heterocycles.

Ionic liquids containing amino acid cations with a positively charged ammonium group are easily prepared by treating the free amino acid or the corresponding alkyl ester with a strong acid; other anions can be introduced by a subsequent ion-exchange step (Scheme 24, routes **B** and **C**).[292–296] This strategy has been applied in the synthesis of amino acid alkyl ester lauryl sulfate surfactants.[297] Alternatively, neutralisation of imidazolium,[298,299] tetra-alkylammonium,[300–302] cholinium[303–307] and tetra-alkylphosphonium hydroxides[308,309] with amino acids provides access to ionic liquids containing amino acid anions with a negatively charged carboxylate group (Scheme 24, route **A**). The hydrophobicity can be increased further by modification of the amino acid alkyl ester, for instance by introducing a trifluoromethane sulfonyl moiety, resulting in a fluorinated imide-type anion (Scheme 24, route **B**).[310] Room temperature ionic liquids derived from alanine and other non-functionalized amino acids often show comparable properties to conventional ionic liquids. However, glutamate and aspartate-based ionic liquids generally have higher glass transition temperatures, melting temperatures and viscosities. These ionic liquids have potential applications in catalysis,[311–317] chiral separations,[299,318–325] gas separation[326–329] and purification,[330] CO_2 absorption,[331–340] oil purification,[341] coal[342] and biomass pre-treatment,[343–351] as bio-lubricants[352–354] and as solvents for organic synthesis, *e.g.* Cu-free Sonogashira coupling reactions[355] or peptide synthesis.[356]



Scheme 24. Strategies in the synthesis of ionic liquids from amino acids: neutralization with base (route **A**); esterification and acidification (route **B**), eventually followed by either modification of the amine and neutralization (left) or anion-exchange (right); acidification with an (in)organic acid (route **C**).

Alternatively, certain amino acids can be modified by alkylation[357] or used as a precursor in the multi-step synthesis of heterocycles, which can in turn be applied as cations in ionic liquids.[315,320,358–360] For instance, the synthesis of chiral imidazolium ionic liquids is illustrated in Scheme 25**A**.[358,361,362] The imidazole ring can be obtained by condensation of the amino acid with formaldehyde, glyoxal and NH_3 under basic conditions. The carboxylic acid moiety is then modified to an alkyl ester and further reduced to an alcohol. Quaternization is finally achieved by N-alkylation of the heterocycle. The chiral imidazolium-based ionic liquids bearing a hydroxyl group on the alkyl chain were isolated with 30-33% yield.[361,362] Recently, a modified though more sustainable approach has been proposed, where the ionic liquid is obtained by hydrothermal decarboxylation of imidazolium zwitterions at 250-300 °C under acidic conditions (Scheme 25**B**).[363] The zwitterions themselves are prepared directly from amino acids, formaldehyde and a bio-based dicarbonyl compound such as glyoxal, pyruvaldehyde or 2,3-butanedione under acidic conditions, in the absence of NH_3 and halogenated reagents.[364] Both steps can even be performed in a one-pot reaction.[363]



Scheme 25. Multi-step synthesis of imidazolium (routes **A** and **B**) and pyridinium cations (route **C**) starting from amino acids and carbohydrate-derived carbonyl compounds.[361,363,365]

Such imidazolium-based ionic liquids have been applied as chiral separation agents,[320] as asymmetric organocatalysts for Michael addition reactions[315] and as precursors for N-heterocyclic carbene Pd catalysts; the latter have been evaluated successfully in Suzuki-Miyaura coupling reactions.[366] In a similar manner pyridinium-based ionic liquids can be produced from renewable resources, for instance by reductive amination of furfural with amino acids, followed by oxidation to the corresponding 3-pyridinol carboxylate zwitterion and subsequent decarboxylation (Scheme 25**C**).[365] Procedures for the synthesis of oxazolinium- and thiazolinium-based ionic liquids have been reported as well.[367,368] Besides the amino acid moiety also functional groups in the side chain can be used as a starting point for ionic liquid synthesis. For instance, the imidazole moiety of histidine can be converted by alkylation to an imidazolium cation.[368,369] Recently, aliphatic amino acids have been involved in the multi-step synthesis of chiral silylated amines; under atmospheric CO_2 pressure the latter react quickly to ammonium carbamates, which behave as reversible ionic liquids.[370]

This approach is most useful for upgrading neutral amino acids, preferably with an aliphatic side chain. Glutamic acid-based ionic liquids generally have a higher glass transition temperature, melting point and viscosity; they might even be solid at room temperature and are therefore often less attractive for common applications as a solvent for cellulose, lignin and other biopolymers.

7 Conclusions and prospects

In the development of a sustainable chemical industry, the conversion of biomass into both fuels and chemicals is of major importance. The variety of highly functionalized components present in biomass provides access to a broad spectrum of high-value chemicals and materials *via* a limited number of transformations. To that end, proteins and amino acids should be considered as raw materials being highly complementary to the more abundant C-, H- and O-containing biomass fractions such as (hemi)cellulose, lignin, lipids and oils. Especially the presence of nitrogen and chiral carbon centers makes them interesting precursors for the production of bio-based fine chemicals.

Millions of tons of amino acids are produced annually and applied in the food, feed and pharmaceutical industry. The fermentative production of amino acids starting from carbohydrates and NH_3 has been optimized by metabolic engineering and strain improvements and is nowadays the most important process. Moreover, since non-edible carbon sources such as glycerol, silage and C_5/C_6 carbohydrates from (hemi)cellulose can be used as well in the fermentation process instead of starch hydrolysates, the use of amino acids in the chemical industry should not be in competition with food supply anymore. Several amino acids are commercially available at fair prices, but efforts are still needed to increase the productivity and to replace conventional nitrogen sources, such as $(NH_4)_2SO_4$ or expensive yeast extracts, by inexpensive renewable resources (*e.g.* peptides). Besides, the generation of substantial amounts of

protein-rich biomass residues can provide many amino acids in bulk quantities at low prices. Protein waste streams with insufficient nutritional quality for feed applications (*e.g.* DDGS) or inherent toxicity (*e.g.* slaughterhouse waste) are potentially interesting feedstocks for the chemical industry.

The valorization chain from protein waste to bio-based chemicals comprises several stages; all these steps can be improved from both economic and environmental point of view. Recent trends are summarized:

(i) protein extraction: traditional techniques are often not useful for protein-rich biomass with higher complexity and hence more extreme conditions are required, thereby increasing the risk of side reactions and waste production. This step can be improved by applying a (bio)chemical and/or mechanical pre-treatment of the biomass.

(ii) protein hydrolysis: harsh (*viz.* highly acidic or basic) conditions are required to achieve complete depolymerization, resulting in amino acid degradation. The development of milder hydrolysis methods is desired. Promising results were already obtained by combining enzymatic and a mildly acidic hydrolysis.

(iii) amino acid separation: traditional techniques, such as extraction or distillation, are inappropriate because of the pH-dependent charge behavior of amino acids in water. However, one should not aim to isolate single compounds, but rather to obtain fractions of amino acids with similar properties such as charge, aromaticity, hydrophobicity and size. Electrodialysis is currently the most promising strategy and enables separating the entire pool of natural amino acids into acidic, basic and neutral fractions. Selective modification of amino acids to products that do not behave as zwitterions in water eventually allows to get around these separation issues. Four strategies are available: (a) reversible modification of one amino acid to an intermediate that can be separated more easily; (b) non-reversible modification or defunctionalization of one amino acid to the desired end product which can also easily be separated from residual amino acids; (c) conversion of an entire amino acid mixture to value-added products which can be isolated by conventional separation techniques; and (d) using the amino acid mixture as such in the final application.

Chemistry delivers a toolbox to convert amino acids into various end products, *e.g.* decarboxylation to amines and nitriles, deamination to carboxylic acids and hydrogenation to amino alcohols, synthesis of fine chemicals and ionic liquids. Catalysts known from petrochemical industrial processes (*e.g.* supported metal catalysts) are once again at the forefront for the conversion of biomass.[10] In this way the amount of (in)organic waste can be reduced substantially, which is beneficial in terms of sustainability. However, catalyst design is of major importance to ensure compatibility with these highly functionalized substrates present in complex (aqueous) media and to improve selectivity and activity. Moreover, catalysts should be resistant against deactivation, poisoning and leaching and they should be easily recovered and regenerated *etc*.

In general, biomass conversion technologies should aim at a maximal retention of functional groups in the end product in order to keep the atom efficiency high. To that end, selective reduction of amino acids to optically active β-amino alcohols is the most appropriate route. By applying a supported bimetallic Rh-MoO_x catalyst under H_2 atmosphere, the reduction can be performed under mild conditions (*e.g.* 80 °C) in aqueous media, thereby producing water as the only by-product. However, the reaction should be performed at high H_2 pressure (*e.g.* 70 bar) in a highly acidic medium to activate the carboxylic acid moiety and temperature and time should be limited to maintain a high enantiomeric excess.

Decarboxylation of amino acids is an attractive tool to recycle nitrogen from biomass directly into nitrogenous compounds, *e.g.* amines, (cyclic) amides or nitriles; the outcome is dependent on the catalyst and the conditions. Amino acid decarboxylases facilitate the conversion of a single amino acid to the corresponding primary amine under mild conditions, thereby enabling the separation of amino acids with a similar isoelectric point. Although these enzymes typically operate in aqueous media under mild conditions (*e.g.* 40 °C), strict control over the pH and additional supply of the expensive cofactor (*viz.* pyridoxal 5'-phosphate) are required to maintain the optimal enzymatic activity. A complementary organocatalytic approach, where α,β-unsaturated carbonyl compounds and particularly isophorone mimic the activity of decarboxylases by forming a Schiff base intermediate with the amino acid, is characterized by a broader substrate scope. However, the system operates in organic solvents and at higher temperatures (*e.g.* 120-270 °C). Alternatively, heterogeneous Pd catalysts facilitate the decarboxylation *via* a direct C-C bond cleavage under inert atmosphere and in aqueous conditions. Since high temperatures (> 225 °C) are required, the substrate scope is however limited to relatively stable cyclic amino acids (*viz.* proline and pyroglutamic acid). In this way glutamic acid can be converted to 2-pyrrolidone and N-alkylated derivatives thereof. Finally, nitriles can be produced by oxidative decarboxylation using either hypobromite species or a supported Ru catalyst and O_2 in aqueous conditions. Hypobromite species can be generated *in situ* from a bromide salt and H_2O_2 by using either haloperoxidases or a supported tungstate catalyst. Again, these (bio)catalytic approaches have the advantage of generating water as the only co-product. The absence of halide waste is an additional advantage of the Ru-catalyzed system, thereby avoiding bromination of aromatic amino acids.

The deamination of amino acids is often considered to be less attractive, since a main asset of the renewable feedstock is lost. However, this is a viable strategy when nitrogen is also recycled into a product with added value, in order to close both the carbon cycle and the nitrogen cycle in a bio-refinery. For instance, proteins have been converted to fuels (alcohols) or chemicals and NH_3. Fuels will eventually end up as CO_2 while NH_3 is recycled as a fertilizer, which can be reused to grow new biomass.[371,372] Enzymatic deamination typically converts one amino acid selectively to an α,β-unsaturated carboxylic acid and NH_3. Reductive deamination of amino acids using supported metal catalysts and H_2 is even more opportune. When the amino acid is modified first by Pd-catalyzed N-alkylation under mild conditions, nitrogen can be recycled as an alkylamine upon selective C-N hydrogenolysis. For instance, supported Pt catalysts were able to convert *N*,*N*-dimethylglutamic acid and -

aspartic acid to the corresponding C_4 and C_5 dimethyl esters and trimethylamine in good to excellent yields. However, the deamination is performed in methanol at 225 °C under 30 bar H_2 and prior water removal is required in terms of selectivity. The development of a catalyst that operates at lower temperatures in water would therefore be desirable.

Amino acids are also useful in the synthesis of fine chemicals and ionic liquids, thereby exploiting the presence of nitrogen or typical molecular features of amino acid side chains. These approaches are typically limited to the neutral amino acid fraction. Additional steps to introduce protecting groups on side chain functionalities are often required in terms of selectivity. The number of synthesis steps should be compensated by the added value of the end product.

Although model systems with single amino acids provide essential information from a fundamental point of view, one should go the extra mile in biomass research and aim to demonstrate the application potential and robustness of a catalytic system by tackling real waste streams with a higher degree of complexity. Crude protein hydrolysates often contain impurities of other biomass constituents, which may affect the catalytic activity. This has been already demonstrated for the oxidative decarboxylation to nitriles[93] and the hydrogenation to amino alcohols.[145] Besides, it could be even more appropriate to use proteins or oligopeptides as precursors for polymer applications. In fact, one should focus more on a simple, one-pot modification of proteins to polymers meeting consumer demands, rather than degrading biopolymers in a multi-step chain to small molecules that eventually serve as monomers for other polymers. The direct incorporation of peptides into biomaterials is highly atom efficient and the chiral properties can be maintained, but these materials are nowadays often associated with low water stability and the physicochemical properties are difficult to control. Oligopeptides consisting of only one amino acid provide better perspectives, but they are nowadays produced by rather inefficient fermentation processes. Consequently, direct modification of an oligopeptide to more controllable functional polymers is highly desirable and might open new opportunities for the polymer industry.

Acknowledgements

F.D.S., L.C. and A.V. are grateful to the Agency for Innovation by Science and Technology (IWT) and Flanders Innovation & Entrepreneurship (VLAIO) for (post)doctoral fellowships (grants 131344 (F.D.S.), HBC.2016.0242/HBC.2017.0366 (L.C.) and 141449 (A.V.)). J.V. thanks Research Foundation Flanders (FWO) for a doctoral fellowship (grant 11Y2615N). D.E.D.V. acknowledges the Flemish government for long-term structural funding (Methusalem grant CASAS), FWO-FNRS for support in the EoS BioFACT project, and FWO for research project funding.

Keywords: protein waste • amino acids • catalysis • bio-refinery • nitrogen recycling

[1] J. Sanders, E. Scott, R. Weusthuis, H. Mooibroek, *Macromol. Biosci.* **2007**, *7*, 105–117.

[2] E. Scott, F. Peter, J. Sanders, *Appl. Microbiol. Biotechnol.* **2007**, *75*, 751–762.

[3] A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411–2502.

[4] M. Dusselier, M. Mascal, B. F. Sels, in *Selective Catalysis for Renewable Feedstocks and Chemicals* (Ed.: K.M. Nicholas), Springer, **2014**, pp. 1–40.

[5] European Commission, "GREEN PAPER A 2030 framework for climate and energy policies," can be found under http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013DC0169, **2017**.

[6] J. J. Bozell, G. R. Petersen, *Green Chem.* **2010**, *12*, 539–554.

[7] R. A. Sheldon, *Green Chem.* **2014**, *16*, 950–963.

[8] C. O. Tuck, E. Perez, I. T. Horvath, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695–699.

[9] G. W. Huber, A. Corma, *Angew. Chem. Int. Ed.* **2007**, *46*, 7184–7201.

[10] M. Besson, P. Gallezot, C. Pinel, *Chem. Rev.* **2014**, *114*, 1827–1870.

[11] P. Gallezot, *Chem. Soc. Rev.* **2012**, *41*, 1538–1558.

[12] T. A. Werpy, G. Petersen, *Top Value Added Chemicals From Biomass: I. Results of Screening for Potential Candidates from Sugars and Synthesis Gas*, U.S. Department of Energy, Richland, WA, **2004**.

[13] M. Ikeda, in *Microbial Production of L-Amino Acids* (Eds.: R. Faurie, J. Thommel, B. Bathe, V.G. Debabov, S. Huebner, M. Ikeda, E. Kimura, A. Marx, B. Möckel, U. Mueller, et al.), Springer, **2003**, pp. 1–35.

[14] W. Leuchtenberger, K. Huthmacher, K. Drauz, *Appl. Microbiol. Biotechnol.* **2005**, *69*, 1–8.

[15] V. DeOliveira, K. Brooks, L. Nogueira, "A Short Introduction to the Distillers' Dried Grains Export Market," can be found under https://agecon.unl.edu/cornhusker-economics/2017/distillers-dried-grain-export-market, **2017**.

[16] Y.-X. Huo, D. G. Wernick, J. C. Liao, *Curr. Opin. Biotechnol.* **2012**, *23*, 406–413.

[17] A. Leip, F. Weiss, J. P. Lesschen, H. Westhoek, *J. Agric. Sci.* **2014**, *152*, 20–33.

[18] T. M. Lammens, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, *Biomass Bioenergy* **2012**, *44*, 168–181.

[19] Grand View Research - Market Research & Consulting, "Global amino acids market by product (L-glutamate, lysine, methionine, threonine, tryptophan, leucine, isoleucine, valine, glutamine, arginine), by source, by application expected to reach USD 35.40 billion by 2022," can be found under http://www.grandviewresearch.com/press-release/global-amino-acids-market, **2015**.

[20] Y. W. Sari, W. J. Mulder, J. P. M. Sanders, M. E. Bruins, *Biotechnol. J.* **2015**, *10*, 1138–1157.

[21] T. Hermann, *J. Biotechnol.* **2003**, *104*, 155–172.

[22] T. Willke, *Appl. Microbiol. Biotechnol.* **2014**, *98*, 9893–9914.

[23] N. Tonouchi, H. Ito, in *Amino Acid Fermentation* (Eds.: A. Yokota, M. Ikeda), Springer, Tokyo, **2016**, pp. 3–14.

[24] R. Krämer, *Food Biotechnol.* **2004**, *18*, 171–216.

[25] W. Leuchtenberger, in *Biotechnology: Products of Primary Metabolism* (Eds.: H.-J. Rehm, G. Reed), **1996**, pp. 466–502.

[26] J. Becker, C. Wittmann, *Curr. Opin. Biotechnol.* **2012**, *23*, 631–640.

[27] J. Becker, C. Wittmann, *Curr. Opin. Biotechnol.* **2012**, *23*, 718–726.

[28] S. Kinoshita, S. Udaka, M. Shimono, *J. Gen. Appl. Microbiol.* **1957**, *3*, 193–205.

[29] K. Ivanov, A. Stoimenova, D. Obreshkova, L. Saso, *Biotechnol. Biotechnol. Equip.* **2013**, *27*, 3620–3626.

[30] M. Khamduang, K. Packdibamrung, J. Chutmanop, Y. Chisti, P. Srinophakun, *J. Ind. Microbiol. Biotechnol.* **2009**, *36*, 1267–1274.

[31] A. Zahoor, S. N. Lindner, V. F. Wendisch, *Comput. Struct. Biotechnol. J.* **2012**, *3*, e201210004.

[32] V. F. Wendisch, J. M. P. Jorge, F. Pérez-García, E. Sgobba, *World J. Microbiol. Biotechnol.* **2016**, *32*, 105.

[33] Q. Xu, S. Li, H. Huang, J. Wen, *Biotechnol. Adv.* **2012**, *30*, 1685–1696.

[34] M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[35] W. Deng, Y. Wang, S. Zhang, K. M. Gupta, M. J. Hülsey, H. Asakura, L. Liu, Y. Han, E. M. Karp, G. T. Beckham, et al., *Proc. Natl. Acad. Sci.* **2018**, *115*, 5093–5098.

[36] C. Sano, *Am. J. Clin. Nutr.* **2009**, *90*, 728S–732S.

[37] R. Belyea, *Bioresour. Technol.* **2004**, *94*, 293–298.

[38] W. Mulder, B. Van den Broek, J. Sanders, M. Bruins, E. Scott, Biobased Economy: De Potentie van Eiwitten Voor Technische Toepassingen, Wageningen UR Food & Biobased Research, Wageningen (The Netherlands), **2012**.

[39] W. Mulder, Proteins in Biomass Streams, Wageningen UR Food & Biobased Research, Wageningen (The Netherlands), **2010**.

[40] C. Martín, A. Moure, G. Martín, E. Carrillo, H. Domínguez, J. C. Parajó, *Biomass Bioenergy* **2010**, *34*, 533–538.

[41] R. S. Lacerda, A. M. Q. B. Bittante, H. Chambi, C. A. Gomide, I. C. F. Moraes, R. A. de Carvalho, P. J. do Amaral Sobral, **2011**, p. 6.

[42] P. G. Dalev, *Bioresour. Technol.* **1994**, *48*, 265–267.

[43] Widyarani, S. C. W. Coulen, J. P. M. Sanders, M. E. Bruins, *Waste Biomass Valorization* **2017**, *8*, 1027–1041.

[44] Biofuels Research Advisory Council, *Biofuels in the European Union - A Vision for 2030 and Beyond*, **2006**.

[45] T. Aspevik, Å. Oterhals, S. B. Rønning, T. Altintzoglou, S. G. Wubshet, A. Gildberg, N. K. Afseth, R. D. Whitaker, D. Lindberg, *Top. Curr. Chem.* **2017**, *375*, 53.

[46] Food and Agriculture Organization of the United Nations, *Food Wastage Footprint: Impacts on Natural Resources*, **2013**.

[47] C. M. Ajila, S. K. Brar, M. Verma, R. D. Tyagi, S. Godbout, J. R. Valéro, *Crit. Rev. Biotechnol.* **2012**, *32*, 382–400.

[48] Y. W. Sari, U. Syafitri, J. P. M. Sanders, M. E. Bruins, *Ind. Crops Prod.* **2015**, *70*, 125–133.

[49] Y. Teng, E. L. Scott, J. P. M. Sanders, *J. Chem. Technol. Biotechnol.* **2012**, *87*, 1458–1465.

[50] Y. Teng, E. L. Scott, J. P. M. Sanders, *Biotechnol. Prog.* **2014**, *30*, 681–688.

[51] Y. W. Sari, M. E. Bruins, J. P. M. Sanders, *Ind. Crops Prod.* **2013**, *43*, 78–83.

[52] C. Zhang, J. P. M. Sanders, T. T. Xiao, M. E. Bruins, *PLoS One* **2015**, *10*, e0133046.

[53] P. dos Santos, M. C. M. M. Ludke, J. V. Ludke, C. B. V. Rabello, M. J. B. dos Santos, T. R. Torres, *Braz. J. Poult. Sci.* **2015**, *17*, 65–71.

[54] B. Bals, B. E. Dale, *Biotechnol. Bioeng.* **2011**, *108*, 530–537.

[55] S. Chiesa, E. Gnansounou, *Bioresour. Technol.* **2011**, *102*, 427–436.

[56] C. Zhang, J. P. M. Sanders, M. E. Bruins, *Biomass Bioenergy* **2014**, *67*, 466–472.

[57] A. Barakat, F. Jérôme, X. Rouau, *ChemSusChem* **2015**, *8*, 1161–1166.

[58] M. Fountoulakis, H. Lahm, *J. Chromatogr. A* **1998**, *826*, 109–134.

[59] I. Rombouts, L. Lamberts, I. Celus, B. Lagrain, K. Brijs, J. A. Delcour, *J. Chromatogr. A* **2009**, *1216*, 5557–5562.

[60] B. J. Meussen, A. N. T. van Zeeland, M. E. Bruins, J. P. M. Sanders, *Food Anal. Methods* **2014**, *7*, 1047–1055.

[61] Y. W. Sari, A. C. Alting, R. Floris, J. P. M. Sanders, M. E. Bruins, *Biomass Bioenergy* **2014**, *67*, 451–459.

[62] R. A. Sheldon, *Adv. Synth. Catal.* **2007**, *349*, 1289–1307.

[63] M. B. A. Kumar, Y. Gao, W. Shen, L. He, *Front. Chem. Sci. Eng.* **2015**, *9*, 295–307.

[64] I. Marcet, C. Álvarez, B. Paredes, M. Díaz, *Waste Manag.* **2016**, *49*, 364–371.

[65] T. Powell, S. Bowra, H. J. Cooper, *Anal. Chem.* **2016**, *88*, 6425–6432.

[66] J. Zhang, S. Zhang, X. Yang, L. Qiu, B. Gao, R. Li, J. Chen, *J. Chem. Technol. Biotechnol.* **2016**, *91*, 483–489.

[67] Widyarani, N. A. Bowden, R. C. Kolfschoten, J. P. M. Sanders, M. E. Bruins, *Ind. Eng. Chem. Res.* **2016**, *55*, 7462–7472.

[68] A. C. Blaga, A.-I. Galaction, D. Cascaval, *Chem. Biochem. Eng. Q.* **2008**, *22*, 439–446.

[69] Ajinomoto, *Process for Obtaining Glutamic Acid Solution from Beet Sugar Waste*, **1961**, GB 868580A.

[70] P. Deblay, M. Minier, H. Renon, *Biotechnol. Bioeng.* **1990**, *35*, 123–131.

[71] B. Tan, G. Luo, J. Wang, *Sep. Purif. Technol.* **2007**, *53*, 330–336.

[72] M. Kumar, B. P. Tripathi, V. K. Shahi, *J. Chem. Technol. Biotechnol.* **2010**, *85*, 648–657.

[73] N. A. Kelly, M. Lukhezo, B. G. Reuben, L. J. Dunne, M. S. Verrall, *J. Chem. Technol. Biotechnol.* **1998**, *72*, 347–355.

[74] E. V. Capela, M. V. Quental, P. Domingues, J. A. P. Coutinho, M. G. Freire, *Green Chem.* **2017**, *19*, 1850–1854.

[75] A. M. Ferreira, H. Passos, A. Okafuji, M. G. Freire, J. A. P. Coutinho, H. Ohno, *Green Chem.* **2017**, *19*, 4012–4016.

[76] I. Kamalanathan, L. Canal, J. Hegarty, V. Najdanovic-Visak, *Fluid Phase Equilib.* **2018**, *462*, 6–13.

[77] H. Yang, L. Chen, C. Zhou, X. Yu, A. E. A. Yagoub, H. Ma, *Food Chem.* **2018**, *245*, 346–352.

[78] B. Van de Voorde, D. Damasceno Borges, F. Vermoortele, R. Wouters, B. Bozbiyik, J. Denayer, F. Taulelle, C. Martineau, C. Serre, G. Maurin, et al., *ChemSusChem* **2015**, *8*, 3159–3166.

[79] D. Jonckheere, J. A. Steele, B. Claes, B. Bueken, L. Claes, B. Lagrain, M. B. J. Roeffaers, D. E. De Vos, *ACS Appl. Mater. Interfaces* **2017**, *9*, 30064–30073.

[80] X. Z. Jin, K. C. Chao, *J. Chem. Eng. Data* **1992**, *37*, 199–203.

[81] L. A. Ferreira, E. A. Macedo, S. P. Pinho, *Chem. Eng. Sci.* **2004**, *59*, 3117–3124.

[82] J. Sandeaux, R. Sandeaux, C. Gavach, H. Grib, T. Sadat, D. Belhocine, N. Mameri, *J. Chem. Technol. Biotechnol.* **1998**, *71*, 267–273.

[83] Y. Hara, *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1373–1376.

[84] K.-I. Kikuchi, T. Gotoh, H. Takahashi, S. Higashino, J. S. Dranoff, *J. Chem. Eng. Jpn.* **1995**, *28*, 103–109.

[85] O. M. Kattan Readi, M. Gironès, K. Nijmeijer, *J. Membr. Sci.* **2013**, *429*, 338–348.

[86] M. Sohn, C.-T. Ho, *J. Agric. Food Chem.* **1995**, *43*, 3001–3003.

[87] Y. Teng, E. L. Scott, A. N. T. van Zeeland, J. P. M. Sanders, *Green Chem.* **2011**, *13*, 624–630.

[88] Y. Teng, E. L. Scott, S. C. M. Witte-van Dijk, J. P. M. Sanders, *New Biotechnol.* **2016**, *33*, 171–178.

[89] O. M. Kattan Readi, H. J. Mengers, W. Wiratha, M. Wessling, K. Nijmeijer, *J. Membr. Sci.* **2011**, *384*, 166–175.

[90] O. M. Kattan Readi, M. Gironès, W. Wiratha, K. Nijmeijer, *Ind. Eng. Chem. Res.* **2013**, *52*, 1069–1078.

[91] O. M. Kattan Readi, E. Rolevink, K. Nijmeijer, *J. Chem. Technol. Biotechnol.* **2014**, *89*, 425–435.

[92] F. De Schouwer, T. Cuypers, L. Claes, D. E. De Vos, *Green Chem.* **2017**, *19*, 1866–1876.

[93] L. Claes, R. Matthessen, I. Rombouts, I. Stassen, T. De Baerdemaeker, D. Depla, J. A. Delcour, B. Lagrain, D. E. De Vos, *ChemSusChem* **2015**, *8*, 345–352.

[94] J.-M. Raquez, M. Deléglise, M.-F. Lacrampe, P. Krawczak, *Prog. Polym. Sci.* **2010**, *35*, 487–509.

[95] F. Song, D. Tang, X.-L. Wang, Y. Wang, *Biomacromolecules* **2011**, *12*, 3369–3380.

[96] R. K. Dhall, *Crit. Rev. Food Sci. Nutr.* **2013**, *53*, 435–450.

[97] W. Shi, M.-J. Dumont, *J. Mater. Sci.* **2014**, *49*, 1915–1930.

[98] M. K. Thakur, V. K. Thakur, R. K. Gupta, A. Pappu, *ACS Sustain. Chem. Eng.* **2016**, *4*, 1–17.

[99] A. Etxabide, J. Uranga, P. Guerrero, K. de la Caba, *Food Hydrocoll.* **2017**, *68*, 192–198.

[100] F. Sanda, T. Endo, *Macromol. Chem. Phys.* **1999**, *200*, 2651–2661.

[101] S. M. Thombre, B. D. Sarwade, *J. Macromol. Sci., Pure Appl. Chem.* **2005**, *42*, 1299–1315.

[102] A. K. Pandey, A. Kumar, *Process Biochem.* **2014**, *49*, 496–505.

[103] H. Mooibroek, N. Oosterhuis, M. Giuseppin, M. Toonen, H. Franssen, E. Scott, J. Sanders, A. Steinbüchel, *Appl. Microbiol. Biotechnol.* **2007**, *77*, 257–267.

[104] G. Galietta, L. Di Gioia, S. Guilbert, B. Cuq, *J. Dairy Sci.* **1998**, *81*, 3123–3130.

[105] V. Tropini, J.-P. Lens, W. J. Mulder, F. Silvestre, *Ind. Crops Prod.* **2004**, *20*, 281–289.

[106] R. A. de Carvalho, C. R. F. Grosso, *Braz. J. Chem. Eng.* **2006**, *23*, 45–53.

[107] V. Perez, M. Felix, A. Romero, A. Guerrero, *Food Bioprod. Process.* **2016**, *97*, 100–108.

[108] K. Muirhead, S. Earnshaw, C. J. Easton, A. Philbrook, *J. Appl. Polym. Sci.* **2012**, *125*, E372–E377.

[109] T. G. Dastidar, A. N. Netravali, *Green Chem.* **2013**, *15*, 3243–3251.

[110] V. K. Thakur, M. R. Kessler, *ACS Sustain. Chem. Eng.* **2014**, *2*, 2454–2460.

[111] M. L. Picchio, R. J. Minari, L. M. Gugliotta, *J. Coatings Technol. Res.* **2017**, *14*, 543–553.

[112] L. Chang, Y. Xue, F. Hsieh, *J. Appl. Polym. Sci.* **2001**, *80*, 10–19.

[113] R. A. West, *Polyol and Method of Making Polyol Using Soy-Based Powder*, **2008**, US 2008/0234458 A1.

[114] G. J. S. Dawes, E. L. Scott, J. Le Nôtre, J. P. M. Sanders, J. H. Bitter, *Green Chem.* **2015**, *17*, 3231–3250.

[115] S. Wang, X. Xu, X. Li, *Chin. J. Org. Chem.* **2018**, *38*, 565–574.

[116] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876.

[117] E. Bieberich, T. Kawaguchi, R. K. Yu, *J. Biol. Chem.* **2000**, *275*, 177–181.

[118] B. Andreeßen, A. Steinbüchel, *AMB Express* **2011**, *1*, 12.

[119] P. S. Metkar, M. A. Scialdone, K. G. Moloy, *Green Chem.* **2014**, *16*, 4575–4586.

[120] P. Karrer, P. Portmann, M. Suter, *Helv. Chim. Acta* **1949**, *32*, 1156–1157.

[121] P. Karrer, B. J. R. Nicolaus, *Helv. Chim. Acta* **1952**, *35*, 1581–1585.

[122] H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada, *Chem. Pharm. Bull.* **1965**, *13*, 995–1000.

[123] R. S. B. Gonçalves, A. C. Pinheiro, E. T. da Silva, J. C. S. da Costa, C. R. Kaiser, M. V. N. de Souza, *Synth. Commun.* **2011**, *41*, 1276–1281.

[124] D. A. Dickman, A. I. Meyers, G. A. Smith, R. E. Gawley, *Org. Synth.* **1985**, *63*, 136.

[125] J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 77.

[126] A. Abiko, S. Masamune, *Tetrahedron Lett.* **1992**, *33*, 5517–5518.

[127] M. J. McKennon, A. I. Meyers, K. Drauz, M. Schwarm, *J. Org. Chem.* **1993**, *58*, 3568–3571.

[128] A. Giannis, K. Sandhoff, *Angew. Chem. Int. Ed.* **1989**, *28*, 218–220.

[129] E. Nicolas, K. C. Russell, V. J. Hruby, *J. Org. Chem.* **1993**, *58*, 766–770.

[130] S.-H. Hwang, M. A. Blaskovich, H.-O. Kim, *Open Org. Chem. J.* **2008**, *2*, 107–109.

[131] W. Kuriyama, Y. Ino, O. Ogata, N. Sayo, T. Saito, *Adv. Synth. Catal.* **2010**, *352*, 92–96.

[132] M. Studer, S. Burkhardt, H.-U. Blaser, *Adv. Synth. Catal.* **2001**, *343*, 802–808.

[133] G. Ovakimian, M. Kuna, P. A. Levene, *J. Biol. Chem.* **1940**, *135*, 91–98.

[134] C. Gao, X. Xiao, D. Mao, G. Lu, *Catal. Sci. Technol.* **2013**, *3*, 1056–1062.

[135] S. Zhang, J. Yu, H. Li, D. Mao, G. Lu, *Sci. Rep.* **2016**, *6*, 33196.

[136] B. Zhan, S. Zhang, J. Yu, X. Xiao, X. Guo, D. Mao, G. Lu, *Catal. Lett.* **2017**, *147*, 2160–2166.

[137] S. Antons, B. Beitzke, *Process for Preparing Optically Active Amino Alcohols*, **1996**, US 5536879 A.

[138] S. Antons, A. S. Tilling, E. Wolters, *Method for Producing Optically Active Amino Alcohols*, **2001**, US 6310254 B1.

[139] W. Mägerlein, C. Dreisbach, H. Hugl, M. K. Tse, M. Klawonn, S. Bhor, M. Beller, *Catal. Today* **2007**, *121*, 140–150.

[140] F. T. Jere, D. J. Miller, J. E. Jackson, *Org. Lett.* **2003**, *5*, 527–530.

[141] K. P. Pimparkar, D. J. Miller, J. E. Jackson, *Ind. Eng. Chem. Res.* **2008**, *47*, 7648–7653.

[142] M. Tamura, R. Tamura, Y. Takeda, Y. Nakagawa, K. Tomishige, *Chem. Commun.* **2014**, *50*, 6656–6659.

[143] M. Tamura, R. Tamura, Y. Takeda, Y. Nakagawa, K. Tomishige, *Chem. Eur. J.* **2015**, *21*, 3097–3107.

[144] B. Sun, G. Süss-Fink, *J. Organomet. Chem.* **2016**, *812*, 81–86.

[145] A. Vandekerkhove, L. Claes, F. De Schouwer, C. Van Goethem, I. F. J. Vankelecom, B. Lagrain, D. E. De Vos, *ACS Sustain. Chem. Eng.* **2018**, *6*, 9218–9228.

[146] J. E. Holladay, T. A. Werpy, D. S. Muzatko, *Appl. Biochem. Biotechnol.* **2004**, *113*, 857–869.

[147] J. E. Holladay, *Process for Chemical Reaction of Amino Acids and Amides Yielding Selective Conversion Products*, **2006**, US 7049446 B2.

[148] P. M. Könst, P. M. C. C. D. Turras, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, *Adv. Synth. Catal.* **2010**, *352*, 1493–1502.

[149] J. Hulsbosch, L. Claes, D. Jonckheere, D. Mestach, D. E. De Vos, *RSC Adv.* **2018**, *8*, 8220–8227.

[150] P. Y. Bruice, *Organic Chemistry 5th Ed.*, Pearson, USA, **2007**.

[151] M. D. Toney, *Biochim. Biophys. Acta, Proteins Proteomics* **2011**, *1814*, 1407–1418.

[152] F. Jordan, H. Patel, *ACS Catal.* **2013**, *3*, 1601–1617.

[153] R. Kourist, J. Guterl, K. Miyamoto, V. Sieber, *ChemCatChem* **2014**, *6*, 689–701.

[154] N. Xu, L. Wei, J. Liu, *World J. Microbiol. Biotechnol.* **2017**, *33*, 64.

[155] N. Yamano, N. Kawasaki, S. Takeda, A. Nakayama, *J. Polym. Environ.* **2013**, *21*, 528–533.

[156] S. J. Park, E. Y. Kim, W. Noh, Y. H. Oh, H. Y. Kim, B. K. Song, K. M. Cho, S. H. Hong, S. H. Lee, J. Jegal, *Bioprocess Biosyst. Eng.* **2013**, *36*, 885–892.

[157] V. Froidevaux, C. Negrell, S. Caillol, J.-P. Pascault, B. Boutevin, *Chem. Rev.* **2016**, *116*, 14181–14224.

[158] J. H. Clark, T. J. Farmer, I. D. V. Ingram, Y. Lie, M. North, *Eur. J. Org. Chem.* **2018**, *2018*, 4265–4271.

[159] H. Seo, J.-H. Kim, J. Jeon, H. Song, S. K. Bhatia, G. Sathiyanarayanan, K. Park, K. J. Kim, S. H. Lee, H. J. Kim, et al., *Process Biochem.* **2016**, *51*, 1413–1419.

[160] S. H. Park, F. Soetyono, H. K. Kim, *J. Microbiol. Biotechnol.* **2017**, *27*, 289–296.

[161] J.-H. Kim, H. Seo, G. Sathiyanarayanan, S. K. Bhatia, H. Song, J. Kim, J. Jeon, J. Yoon, Y. Kim, K. Park, et al., *J. Ind. Eng. Chem.* **2017**, *46*, 44–48.

[162] S. Kind, W. K. Jeong, H. Schröder, C. Wittmann, *Metab. Eng.* **2010**, *12*, 341–351.

[163] S. Kind, S. Kreye, C. Wittmann, *Metab. Eng.* **2011**, *13*, 617–627.

[164] M. Li, D. Li, Y. Huang, M. Liu, H. Wang, Q. Tang, F. Lu, *J. Ind. Microbiol. Biotechnol.* **2014**, *41*, 701–709.

[165] W. Ma, W. Cao, B. Zhang, K. Chen, Q. Liu, Y. Li, P. Ouyang, *Sci. Rep.* **2015**, *5*, 15630.

[166] H. Sagong, K. Kim, *PLoS One* **2017**, *12*, e0170163.

[167] J.-H. Kim, J. Kim, H.-J. Kim, G. Sathiyanarayanan, S. K. Bhatia, H. Song, Y. Choi, Y. Kim, K. Park, Y.-H. Yang, *Enzyme Microb. Technol.* **2017**, *104*, 9–15.

[168] S. Jeong, Y. J. Yeon, E. Choi, S. Byun, D. Cho, I. K. Kim, Y. H. Kim, *Korean J. Chem. Eng.* **2016**, *33*, 1530–1533.

[169] J. Wang, J. Mao, W. Tian, G. Wei, S. Xu, W. Ma, K. Chen, M. Jiang, P. Ouyang, *Green Chem.* **2018**, *20*, 2880–2887.

[170] T. MIMITSUKA, H. SAWAI, M. HATSU, K. YAMADA, *Biosci. Biotechnol. Biochem.* **2007**, *71*, 2130–2135.

[171] T. Tateno, Y. Okada, T. Tsuchidate, T. Tanaka, H. Fukuda, A. Kondo, *Appl. Microbiol. Biotechnol.* **2009**, *82*, 115–121.

[172] D. H. Kwak, H. G. Lim, J. Yang, S. W. Seo, G. Y. Jung, *Biotechnol. Biofuels* **2017**, *10*, 20.

[173] N. Ikeda, M. Miyamoto, N. Adachi, M. Nakano, T. Tanaka, A. Kondo, *AMB Express* **2013**, *3*, 67.

[174] K. Imao, R. Konishi, M. Kishida, Y. Hirata, S. Segawa, N. Adachi, R. Matsuura, Y. Tsuge, T. Matsumoto, T. Tanaka, et al., *Bioresour. Technol.* **2017**, *245*, 1684–1691.

[175] S. K. Bhatia, Y. H. Kim, H. J. Kim, H.-M. Seo, J.-H. Kim, H.-S. Song, G. Sathiyanarayanan, S.-H. Park, K. Park, Y.-H. Yang, *Bioprocess Biosyst. Eng.* **2015**, *38*, 2315–2322.

[176] P. M. Könst, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, *Green Chem.* **2011**, *13*, 1167–1174.

[177] Y. Shen, L. Zhao, Y. Li, L. Zhang, G. Shi, *Biotechnol. Lett.* **2014**, *36*, 1681–1686.

[178] T. M. Lammens, D. De Biase, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, *Green Chem.* **2009**, *11*, 1562–1567.

[179] K. Dose, *Chem. Ber.* **1957**, *90*, 1251–1258.

[180] M. Malherbe, G. Chatelus, *C. R. Acad. Sci.* **1971**, *272*, 1237–1240.

[181] M. Hashimoto, Y. Eda, Y. Osanai, T. Iwai, S. Aoki, *Chem. Lett.* **1986**, *15*, 893–896.

[182] A. Lawson, *Process for the Production of Amines*, **1965**, GB 1008594.

[183] D. M. Jackson, R. L. Ashley, C. B. Brownfield, D. R. Morrison, R. W. Morrison, *Synth. Commun.* **2015**, *45*, 2691–2700.

[184] F. G. Baddar, S. A. M. Sherif, *J. Chem. Soc.* **1956**, 4292–4295.

[185] K. Dose, *Nature* **1957**, *179*, 734–735.

[186] G. G. de la Moricière, G. Chatelus, *Bull. Soc. Chim. Fr.* **1969**, 4421–4425.

[187] L. Claes, Catalytic Strategies for Decarboxylation of Amino Acids, KU Leuven, **2016**.

[188] G. Chatelus, *Bull. Soc. Chim. Fr.* **1964**, *408*, 2523–2532.

[189] M. Hartmann, M. Seiberth, *Helv. Chim. Acta* **1932**, *15*, 1390–1392.

[190] S. Wallbaum, T. Mehler, J. Martens, *Synth. Commun.* **1994**, *24*, 1381–1387.

[191] M. Toumi, F. Couty, G. Evano, *Tetrahedron Lett.* **2008**, *49*, 1175–1179.

[192] S. D. Brandt, D. Mansell, S. Freeman, I. A. Fleet, J. F. Alder, *J. Pharm. Biomed. Anal.* **2006**, *41*, 872–882.

[193] C. P. B. Martins, M. A. Awan, S. Freeman, T. Herraiz, J. F. Alder, S. D. Brandt, *J. Chromatogr. A* **2008**, *1210*, 115–120.

[194] D. Fontanilla, M. Johannessen, A. R. Hajipour, N. V. Cozzi, M. B. Jackson, A. E. Ruoho, *Science* **2009**, *323*, 934–937.

[195] S. Takano, T. Nishimura, K. Ogasawara, *Heterocycles* **1977**, *6*, 1167–1171.

[196] M. Omeis, G. Koehler, M. Neumann, T. Kuebelbaeck, *Continuous*

Process for Decarboxylating Carboxylic Acids, **2009**, US 7485756 B2.

[197] C. Cassani, G. Bergonzini, C. Wallentin, *Org. Lett.* **2014**, *16*, 4228–4231.

[198] S. Cadot, N. Rameau, S. Mangematin, C. Pinel, L. Djakovitch, *Green Chem.* **2014**, *16*, 3089–3097.

[199] F. De Schouwer, L. Claes, N. Claes, S. Bals, J. Degrève, D. E. De Vos, *Green Chem.* **2015**, *17*, 2263–2270.

[200] A. L. Harreus, R. Backers, J.-O. Eichler, R. Feuerhake, C. Jäkel, U. Mahn, R. Pinkos, R. Vogelsang, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, **2011**, pp. 1–7.

[201] L. E. Manzer, *Production of 5-Methyl-N-Aryl-2-Pyrrolidone and 5-Methyl-N-Alkyl-2pyrrolidone by Reductive Amination of Levulinic Acid with Nitro Compounds*, **2004**, US 6818593 B2.

[202] B. Vandeputte, K. Moonen, P. Roose, *Use of Improved N-Alkyl Pyrrolidone Solvents*, **2013**, WO 2013/107822 A1.

[203] J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmer, A. J. Hunt, *Green Chem.* **2016**, *18*, 3990–3996.

[204] ECHA, *REACH "Candidate List of Substances of Very High Concern for Authorisation,"* **2017**.

[205] F. De Schouwer, S. Adriaansen, L. Claes, D. E. De Vos, *Green Chem.* **2017**, *19*, 4919–4929.

[206] J. Verduyckt, M. Van Hoof, F. De Schouwer, M. Wolberg, M. Kurttepeli, P. Eloy, E. M. Gaigneaux, S. Bals, C. E. A. Kirschhock, D. E. De Vos, *ACS Catal.* **2016**, *6*, 7303–7310.

[207] J. Verduyckt, R. Coeck, D. E. De Vos, *ACS Sustain. Chem. Eng.* **2017**, *5*, 3290–3295.

[208] G. W. Stevenson, J. M. Luck, *J. Biol. Chem.* **1961**, *236*, 715–717.

[209] G. Laval, B. T. Golding, *Synlett* **2003**, *4*, 0542–0546.

[210] H. D. Dakin, *Biochem. J.* **1916**, *10*, 319–323.

[211] H. D. Dakin, *Biochem. J.* **1917**, *11*, 79–95.

[212] G. A. Hiegel, J. C. Lewis, J. W. Bae, *Synth. Commun.* **2004**, *34*, 3449–3453.

[213] L. De Luca, G. Giacomelli, *Synlett* **2004**, *12*, 2180–2184.

[214] A. H. Friedman, S. Morgulis, *J. Am. Chem. Soc.* **1936**, *58*, 909–913.

[215] W. H. McGregor, F. H. Carpenter, *Biochemistry* **1962**, *1*, 53–60.

[216] E. V. Bellale, S. N. Huddar, U. S. Mahajan, K. G. Akamanchi, *Pure Appl. Chem.* **2011**, *83*, 607–612.

[217] J. Le Nôtre, E. L. Scott, M. C. R. Franssen, J. P. M. Sanders, *Green Chem.* **2011**, *13*, 807–809.

[218] T. Shono, Y. Matsumura, K. Inoue, *J. Am. Chem. Soc.* **1984**, *106*, 6075–6076.

[219] J. Dai, Y. Huang, C. Fang, Q. Guo, Y. Fu, *ChemSusChem* **2012**, *5*, 617–620.

[220] R. Matthessen, L. Claes, J. Fransaer, K. Binnemans, D. E. De Vos, *Eur. J. Org. Chem.* **2014**, *2014*, 6649–6652.

[221] M. Nieder, L. Hager, *Arch. Biochem. Biophys.* **1985**, *240*, 121–127.

[222] A. But, J. Le Nôtre, E. L. Scott, R. Wever, J. P. M. Sanders, *ChemSusChem* **2012**, *5*, 1199–1202.

[223] A. But, E. van der Wijst, J. Le Nôtre, R. Wever, J. P. M. Sanders, J. H. Bitter, E. L. Scott, *Green Chem.* **2017**, *19*, 5178–5186.

[224] A. But, A. van Noord, F. Poletto, J. P. M. Sanders, M. C. R. Franssen, E. L. Scott, *Mol. Catal.* **2017**, *443*, 92–100.

[225] L. Claes, J. Verduyckt, I. Stassen, B. Lagrain, D. E. De Vos, *Chem. Commun.* **2015**, *51*, 6528–6531.

[226] T. M. Lammens, J. Le Nôtre, M. C. R. Franssen, E. L. Scott, J. P. M. Sanders, *ChemSusChem* **2011**, *4*, 785–791.

[227] T. M. Lammens, J. Potting, J. P. M. Sanders, I. J. M. De Boer, *Environ. Sci. Technol.* **2011**, *45*, 8521–8528.

[228] M. M. Heberling, B. Wu, S. Bartsch, D. B. Janssen, *Curr. Opin. Chem. Biol.* **2013**, *17*, 250–260.

[229] B. M. Nestl, S. C. Hammer, B. A. Nebel, B. Hauer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3070–3095.

[230] S. Bartsch, U. T. Bornscheuer, *Angew. Chem. Int. Ed.* **2009**, *48*, 3362–3365.

[231] Persistence Market Research, "Cinnamic Acid Market: Global Industry Analysis and Forecast to 2015 to 2021," can be found under https://www.persistencemarketresearch.com/market-research/cinnamic-acid-market.asp, **2017**.

[232] S. Y. Ou, J. W. Teng, Y. Y. Zhao, J. Zhao, in *Phenolic Acids: Composition, Applications and Health Benefits* (Ed.: S. Munné-Bosch), **2012**, pp. 63–71.

[233] Q. Li, J. Xing, in *Production of Platform Chemicals from Renewable Resources* (Eds.: Z. Fang, R.L. Smith, X. Qi), Springer Singapore, Singapore, **2017**, pp. 231–262.

[234] R. McKenna, D. R. Nielsen, *Metab. Eng.* **2011**, *13*, 544–554.

[235] E. Nomura, A. Hosoda, H. Mori, H. Taniguchi, *Green Chem.* **2005**, *7*, 863–866.

[236] J. Spekreijse, J. Le Nôtre, J. van Haveren, E. L. Scott, J. P. M. Sanders, *Green Chem.* **2012**, *14*, 2747–2751.

[237] A. V. Pukin, C. G. Boeriu, E. L. Scott, J. P. M. Sanders, M. C. R. Franssen, *J. Mol. Catal. B: Enzym.* **2010**, *65*, 58–62.

[238] S. J. Park, Y. H. Oh, W. Noh, H. Y. Kim, J. H. Shin, E. G. Lee, S. Lee, Y. David, M. G. Baylon, B. K. Song, et al., *Biotechnol. J.* **2014**, *9*, 1322–1328.

[239] X. Wang, P. Cai, K. Chen, P. Ouyang, *J. Mol. Catal. B: Enzym.* **2016**, *134*, 115–121.

[240] P. Liu, H. Zhang, M. Lv, M. Hu, Z. Li, C. Gao, P. Xu, C. Ma, *Sci. Rep.* **2015**, *4*, 5657.

[241] C. M. Rohles, G. Gießelmann, M. Kohlstedt, C. Wittmann, J. Becker, *Microb. Cell Fact.* **2016**, *15*, 154.

[242] J. R. L. Smith, D. I. Richards, C. B. Thomas, M. Whittaker, *J. Chem. Soc., Perkin Trans. 2* **1985**, *0*, 1677–1682.

[243] M. T. Musser, E. I. D. De Nemours, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, **2000**, pp. 1–11.

[244] A. Tullo, *Chem. Eng. News* **2002**, *80*, 13.

[245] T. R. Boussie, E. L. Dias, Z. M. Fresco, V. J. Murphy, *Production of Glutaric Acid and Derivatives from Carbohydrate-Containing Materials*, **2014**, US 2014/0350297 A1.

[246] R. J. W. Cremlyn, R. M. Ellam, T. K. Mitra, *J. Chem. Soc. C* **1971**, 1647–1651.

[247] J. H. Markgraf, H. A. Davis, *J. Chem. Educ.* **1990**, *67*, 173–174.

[248] W. Zhang, M.-Y. Rao, Z.-J. Cheng, X.-Y. Zhu, K. Gao, J. Yang, B. Yang, X.-L. Liao, *Chem. Pap.* **2015**, *69*, 716–721.

[249] D. A. Wicks, *Methods of Making Cyclic Amide Monomers, and Related Derivatives and Methods*, **2010**, WO 2010/011967 A1.

[250] G. A. Doldouras, J. Kollonitsch, *J. Am. Chem. Soc.* **1978**, *100*, 341–342.

[251] T. V. Ramamurthy, K. V. Viswanathan, K. N. Rao, *J. Label. Compd. Radiopharm.* **1982**, *19*, 899–903.

[252] T. V. Ramamurthy, S. Ravi, K. V. Viswanathan, *J. Label. Compd. Radiopharm.* **1988**, *25*, 809–814.

[253] J. W. Frost, *Synthesis of Caprolactam from Lysine*, **2005**, WO 2005/123669 A1.

[254] J. Yang, Convenient Synthesis of Caprolactam from Lysine: Alternative of Current Benzene-Based Caprolactam Production, Michigan State University, **2007**.

[255] J. W. Frost, *Catalytic Deamination for Caprolactam Production*, **2012**, US 8283466 B2.

[256] M. Cattenot, E. Peeters, C. Geantet, E. Devers, J. L. Zotin, *Catal. Lett.* **2005**, *99*, 171–176.

[257] *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, **2011**.

[258] Q. Wang, C. Wan, Y. Gu, J. Zhang, L. Gao, Z. Wang, *Green Chem.* **2011**, *13*, 578–581.

[259] J.-C. Xiang, M. Wang, Y. Cheng, A.-X. Wu, *Org. Lett.* **2016**, *18*, 24–27.

[260] J.-C. Xiang, Y. Cheng, Z.-X. Wang, J.-T. Ma, M. Wang, B.-C. Tang, Y.-D. Wu, A.-X. Wu, *Org. Lett.* **2017**, *19*, 2997–3000.

[261] Y. Cheng, J.-C. Xiang, Z.-X. Wang, J.-T. Ma, M. Wang, B.-C. Tang, Y.-D. Wu, Y.-P. Zhu, A.-X. Wu, *Adv. Synth. Catal.* **2018**, *360*, 550–555.

[262] I. Romero-Estudillo, V. R. Batchu, A. Boto, *Adv. Synth. Catal.* **2014**, *356*, 3742–3748.

[263] W. Xu, U. Kloeckner, B. J. Nachtsheim, *J. Org. Chem.* **2013**, *78*, 6065–6074.

[264] Y. Yan, Z. Wang, *Chem. Commun.* **2011**, *47*, 9513–9515.

[265] W. Xu, H. Fu, *J. Org. Chem.* **2011**, *76*, 3846–3852.

[266] J.-C. Xiang, Z.-X. Wang, Y. Cheng, S.-Q. Xia, M. Wang, B.-C. Tang, Y.-D. Wu, A. Wu, *J. Org. Chem.* **2017**, *82*, 9210–9216.

[267] H. Wang, W. Xu, L. Xin, W. Liu, Z. Wang, K. Xu, *J. Org. Chem.* **2016**, *81*, 3681–3687.

[268] Q. Wang, S. Zhang, F. Guo, B. Zhang, P. Hu, Z. Wang, *J. Org. Chem.* **2012**, *77*, 11161–11166.

[269] H. Liu, X. Wang, C. Ma, *Synthesis* **2018**, *50*, 2761–2767.

[270] R.-H. Chen, J.-F. Xiong, P. Peng, G.-Z. Mo, X.-S. Tang, Z.-Y. Wang, X.-F. Wang, *Asian J. Chem.* **2014**, *26*, 926–932.

[271] S. Luo, J. K. De Brabander, *Tetrahedron Lett.* **2015**, *56*, 3179–3182.

[272] A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602–11605.

[273] A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624–627.

[274] Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437–440.

[275] Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 5257–5260.

[276] Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832–1835.

[277] R. A. Garza-Sanchez, A. Tlahuext-Aca, G. Tavakoli, F. Glorius, *ACS Catal.* **2017**, *7*, 4057–4061.

[278] K. A. Margrey, A. Levens, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2017**, *56*, 15644–15648.

[279] H. Bi, W. Chen, Y. Liang, C. Li, *Org. Lett.* **2009**, *11*, 3246–3249.

[280] H. Bi, L. Zhao, Y. Liang, C. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 792–795.

[281] H. Bi, Q. Teng, M. Guan, W. Chen, Y. Liang, X. Yao, C. Li, *J. Org. Chem.* **2010**, *75*, 783–788.

[282] Y. Jin, M. Jiang, H. Wang, H. Fu, *Sci. Rep.* **2016**, *6*, 20068.

[283] W. Cheng, R. Shang, Y. Fu, *ACS Catal.* **2017**, *7*, 907–911.

[284] R. Madhavachary, Q. Wang, A. Dömling, *Chem. Commun.* **2017**, *53*, 8549–8552.

[285] S. S. Schweiker, W. A. Loughlin, A. S. Lohning, M. J. Petersson, I. D. Jenkins, *Eur. J. Med. Chem.* **2014**, *84*, 584–594.

[286] J. Plaquevent, J. Levillain, F. Guillen, C. Malhiac, A.-C. Gaumont, *Chem. Rev.* **2008**, *108*, 5035–5060.

[287] J. Hulsbosch, D. E. De Vos, K. Binnemans, R. Ameloot, *ACS Sustain. Chem. Eng.* **2016**, *4*, 2917–2931.

[288] K. S. Egorova, M. M. Seitkalieva, A. V Posvyatenko, V. P. Ananikov, *Toxicol. Res. (Camb.)* **2015**, *4*, 152–159.

[289] X. Hou, Q. Liu, T. J. Smith, N. Li, M. Zong, *PLoS One* **2013**, *8*, e59145.

[290] A. Jordan, N. Gathergood, *Chem. Soc. Rev.* **2015**, *44*, 8200–8237.

[291] A. Jordan, A. Haiß, M. Spulak, Y. Karpichev, K. Kümmerer, N. Gathergood, *Green Chem.* **2016**, *18*, 4374–4392.

[292] G. Tao, L. He, N. Sun, Y. Kou, *Chem. Commun.* **2005**, *28*, 3562–3564.

[293] G. Tao, L. He, W. Liu, L. Xu, W. Xiong, T. Wang, Y. Kou, *Green Chem.* **2006**, *8*, 639–646.

[294] L. Zhang, L. He, C. Hong, S. Qin, G. Tao, *Green Chem.* **2015**, *17*, 5154–5163.

[295] H. Rong, W. Li, Z. Chen, X. Wu, *J. Phys. Chem. B* **2008**, *112*, 1451–1455.

[296] G. Imperato, B. König, C. Chiappe, *Eur. J. Org. Chem.* **2007**, *2007*, 1049–1058.

[297] T. J. Trivedi, K. S. Rao, T. Singh, S. K. Mandal, N. Sutradhar, A. B. Panda, A. Kumar, *ChemSusChem* **2011**, *4*, 604–608.

[298] K. Fukumoto, M. Yoshizawa, H. Ohno, *J. Am. Chem. Soc.* **2005**, *127*, 2398–2399.

[299] F. Tang, Q. Zhang, D. Ren, Z. Nie, Q. Liu, S. Yao, *J. Chromatogr. A* **2010**, *1217*, 4669–4674.

[300] Y. Jiang, G. Wang, Z. Zhou, Y. Wu, J. Geng, Z. Zhang, *Chem. Commun.* **2008**, *0*, 505–507.

[301] M. B. A. Rahman, K. Jumbri, M. Basri, E. Abdulmalek, K. Sirat, A. B. Salleh, *Molecules* **2010**, *15*, 2388–2397.

[302] C. R. Allen, P. L. Richard, A. J. Ward, L. G. A. van de Water, A. F. Masters, T. Maschmeyer, *Tetrahedron Lett.* **2006**, *47*, 7367–7370.

[303] P. Moriel, E. J. García-Suárez, M. Martínez, A. B. García, M. A. Montes-Morán, V. Calvino-Casilda, M. A. Bañares, *Tetrahedron Lett.* **2010**, *51*, 4877–4881.

[304] Q. Liu, X. Hou, N. Li, M. Zong, *Green Chem.* **2012**, *14*, 304–307.

[305] D. Tao, Z. Cheng, F.-F. Chen, Z. Li, N. Hu, X. Chen, *J. Chem. Eng. Data* **2013**, *58*, 1542–1548.

[306] S. De Santis, G. Masci, F. Casciotta, R. Caminiti, E. Scarpellini, M. Campetella, L. Gontrani, *Phys. Chem. Chem. Phys.* **2015**, *17*, 20687–20698.

[307] S. Zhang, L. Ma, P. Wen, X. Ye, R. Dong, W. Sun, M. Fan, D. Yang, F. Zhou, W. Liu, *Tribol. Int.* **2018**, *121*, 435–441.

[308] J. Kagimoto, K. Fukumoto, H. Ohno, *Chem. Commun.* **2006**, *0*, 2254–2256.

[309] H. Ohno, K. Fukumoto, *Acc. Chem. Res.* **2007**, *40*, 1122–1129.

[310] K. Fukumoto, H. Ohno, *Chem. Commun.* **2006**, *0*, 3081–3083.

[311] S. P. Bahekar, N. R. Agrawal, P. B. Sarode, A. R. Agrawal, H. S. Chandak, *ChemistrySelect* **2017**, *2*, 9326–9329.

[312] W. Chen, Y. Zhang, L. Zhu, J. Lan, R. Xie, J. You, *J. Am. Chem. Soc.* **2007**, *129*, 13879–13886.

[313] N. Ferlin, M. Courty, A. N. Van Nhien, S. Gatard, M. Pour, B. Quilty, M. Ghavre, A. Haiß, K. Kümmerer, N. Gathergood, et al., *RSC Adv.* **2013**, *3*, 26241–26251.

[314] X.-D. Lang, S. Zhang, Q.-W. Song, L.-N. He, *RSC Adv.* **2015**, *5*, 15668–15673.

[315] S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J. Cheng, *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097.

[316] K. R. Roshan, T. Jose, D. Kim, K. A. Cherian, D. W. Park, *Catal. Sci. Technol.* **2014**, *4*, 963–970.

[317] J. Yan, L. Wang, *Synthesis* **2010**, *2010*, 447–452.

[318] Q. Liu, K. Wu, F. Tang, L. Yao, F. Yang, Z. Nie, S. Yao, *Chem. Eur. J.* **2009**, *15*, 9889–9896.

[319] Y. Liu, A. Tian, X. Wang, J. Qi, F. Wang, Y. Ma, Y. Ito, Y. Wei, *J. Chromatogr. A* **2015**, *1400*, 40–46.

[320] L. González, B. Altava, M. Bolte, M. I. Burguete, E. García-Verdugo, S. V. Luis, *Eur. J. Org. Chem.* **2012**, *2012*, 4996–5009.

[321] J. Zhang, Y. Du, Q. Zhang, J. Chen, G. Xu, T. Yu, X. Hua, *J. Chromatogr. A* **2013**, *1316*, 119–126.

[322] W. Yujiao, W. Guoyan, Z. Wenyan, Z. Hongfen, J. Huanwang, C. Anjia, *Biomed. Chromatogr.* **2014**, *28*, 610–614.

[323] D. Wu, Q. Yin, P. Cai, X. Zhao, Y. Pan, *Anal. Chim. Acta* **2017**, *962*, 97–103.

[324] J. Wahl, U. Holzgrabe, *J. Pharm. Biomed. Anal.* **2018**, *148*, 245–250.

[325] X. Mu, L. Qi, H. Zhang, Y. Shen, J. Qiao, H. Ma, *Talanta* **2012**, *97*, 349–354.

[326] F. Moghadam, E. Kamio, A. Yoshizumi, H. Matsuyama, *Chem. Commun.* **2015**, *51*, 13658–13661.

[327] F. Moghadam, E. Kamio, H. Matsuyama, *J. Membr. Sci.* **2017**, *525*, 290–297.

[328] S. Kasahara, E. Kamio, T. Ishigami, H. Matsuyama, *Chem. Commun.* **2012**, *48*, 6903–6905.

[329] S. Kasahara, E. Kamio, A. Yoshizumi, H. Matsuyama, *Chem. Commun.* **2014**, *50*, 2996–2999.

[330] B. Wang, K. Zhang, S. Ren, Y. Hou, W. Wu, *RSC Adv.* **2016**, *6*, 101462–101469.

[331] B. E. Gurkan, J. C. de la Fuente, E. M. Mindrup, L. E. Ficke, B. F. Goodrich, E. A. Price, W. F. Schneider, J. F. Brennecke, *J. Am. Chem. Soc.* **2010**, *132*, 2116–2117.

[332] Z. Feng, M. Jing-Wen, Z. Zheng, W. You-Ting, Z. Zhi-Bing, *Chem. Eng. J.* **2012**, *181–182*, 222–228.

[333] X. Wang, N. G. Akhmedov, Y. Duan, D. Luebke, D. Hopkinson, B. Li, *ACS Appl. Mater. Interfaces* **2013**, *5*, 8670–8677.

[334] X. Wang, N. G. Akhmedov, Y. Duan, D. Luebke, B. Li, *J. Mater. Chem. A* **2013**, *1*, 2978–2982.

[335] Q. Yang, Z. Wang, Z. Bao, Z. Zhang, Y. Yang, Q. Ren, H. Xing, S. Dai, *ChemSusChem* **2016**, *9*, 806–812.

[336] Z. Feng, G. Yuan, W. Xian-Kun, M. Jing-Wen, W. You-Ting, Z. Zhi-Bing, *Chem. Eng. J.* **2013**, *223*, 371–378.

[337] Y. Gao, F. Zhang, K. Huang, J.-W. Ma, Y.-T. Wu, Z.-B. Zhang, *Int. J. Greenh. Gas Control* **2013**, *19*, 379–386.

[338] J. Guzmán, C. Ortega-Guevara, R. G. de León, R. Martínez-Palou, *Chem. Eng. Technol.* **2017**, *40*, 2339–2345.

[339] B. Lv, G. Jing, Y. Qian, Z. Zhou, *Chem. Eng. J.* **2016**, *289*, 212–218.

[340] J. Ma, Z. Zhou, F. Zhang, C. Fang, Y. Wu, Z. Zhang, A. Li, *Environ. Sci. Technol.* **2011**, *45*, 10627–10633.

[341] K. Anderson, P. Goodrich, C. Hardacre, A. Hussain, D. W. Rooney, D. Wassell, *Fuel* **2013**, *108*, 715–722.

[342] T. Q. To, K. Shah, P. Tremain, B. A. Simmons, B. Moghtaderi, R. Atkin, *Fuel* **2017**, *202*, 296–306.

[343] X.-D. Hou, T. J. Smith, N. Li, M.-H. Zong, *Biotechnol. Bioeng.* **2012**, *109*, 2484–2493.

[344] X.-D. Hou, N. Li, M.-H. Zong, *Biotechnol. Bioeng.* **2013**, *110*, 1895–1902.

[345] X.-D. Hou, N. Li, M.-H. Zong, *Bioresour. Technol.* **2013**, *136*, 469–474.

[346] X.-D. Hou, N. Li, M.-H. Zong, *ACS Sustain. Chem. Eng.* **2013**, *1*, 519–526.

[347] X.-D. Hou, J. Xu, N. Li, M.-H. Zong, *Biotechnol. Bioeng.* **2015**, *112*, 65–73.

[348] K. Ohira, Y. Abe, M. Kawatsura, K. Suzuki, M. Mizuno, Y. Amano, T. Itoh, *ChemSusChem* **2012**, *5*, 388–391.

[349] Y. Hamada, K. Yoshida, R. Asai, S. Hayase, T. Nokami, S. Izumi, T. Itoh, *Green Chem.* **2013**, *15*, 1863–1868.

[350] J. Tao, T. Kishimoto, M. Hamada, N. Nakajima, *Holzforschung* **2016**, *70*, 911–917.

[351] Z. Zhao, Y. Yang, A. A. Abdeltawab, S. M. Yakout, X. Chen, G. Yu, *Bioresour. Technol.* **2017**, *245*, 625–632.

[352] P. K. Khatri, G. D. Thakre, S. L. Jain, *Ind. Eng. Chem. Res.* **2013**, *52*, 15829–15837.

[353] Z. Song, Y. Liang, M. Fan, F. Zhou, W. Liu, *RSC Adv.* **2014**, *4*, 19396–19402.

[354] P. Nagendramma, P. K. Khatri, G. D. Thakre, S. L. Jain, *J. Mol. Liq.* **2017**, *244*, 219–225.

[355] T. Fukuyama, M. T. Rahman, S. Maetani, I. Ryu, *Chem. Lett.* **2011**, *40*, 1027–1029.

[356] S. Furukawa, T. Fukuyama, A. Matsui, M. Kuratsu, R. Nakaya, T. Ineyama, H. Ueda, I. Ryu, *Chem. Eur. J.* **2015**, *21*, 11980–11983.

[357] L. He, G. Tao, D. A. Parrish, J. M. Shreeve, *J. Phys. Chem. B* **2009**, *113*, 15162–15169.

[358] H. Clavier, L. Boulanger, N. Audic, L. Toupet, M. Mauduit, J.-C. Guillemin, *Chem. Commun.* **2004**, *4*, 1224–1225.

[359] D. Coleman, M. Špulák, M. T. Garcia, N. Gathergood, *Green Chem.* **2012**, *14*, 1350–1356.

[360] X. Chen, X. Li, A. Hu, F. Wang, *Tetrahedron: Asymmetry* **2008**, *19*, 1–14.

[361] W. Bao, Z. Wang, Y. Li, *J. Org. Chem.* **2003**, *68*, 591–593.

[362] J. Ding, D. W. Armstrong, *Chirality* **2005**, *17*, 281–292.

[363] S. Kirchhecker, M. Antonietti, D. Esposito, *Green Chem.* **2014**, *16*, 3705–3709.

[364] D. Esposito, S. Kirchhecker, M. Antonietti, *Chem. Eur. J.* **2013**, *19*, 15097–15100.

[365] S. Kirchhecker, S. Tröger-Müller, S. Bake, M. Antonietti, A. Taubert, D. Esposito, *Green Chem.* **2015**, *17*, 4151–4156.

[366] E. Steeples, A. Kelling, U. Schilde, D. Esposito, *New J. Chem.* **2016**, *40*, 4922–4930.

[367] P. Wasserscheid, A. Bösmann, C. Bolm, *Chem. Commun.* **2002**, *3*, 200–201.

[368] D. Brégeon, J. Levillain, F. Guillen, J.-C. Plaquevent, A.-C. Gaumont, *Amino Acids* **2008**, *35*, 175–184.

[369] F. Guillen, D. Brégeon, J. Plaquevent, *Tetrahedron Lett.* **2006**, *47*, 1245–1248.

[370] L. Bouchardy, V. Rodriguez-Ruiz, C. Bournaud, F.-D. Boyer, M. Toffano, P. Judeinstein, G. Vo-Thanh, *ChemistrySelect* **2018**, *3*, 958–962.

[371] Y. Huo, K. M. Cho, J. G. L. Rivera, E. Monte, C. R. Shen, Y. Yan, J. C. Liao, *Nat. Biotechnol.* **2011**, *29*, 346–351.

[372] D. G. Wernick, J. C. Liao, *Appl. Microbiol. Biotechnol.* **2013**, *97*, 1397–1406.

Entry for the Table of Contents

Layout 1:

REVIEW

Getting value out of waste! Chemistry and catalysis offer an excellent toolbox to produce valuable commodity and fine chemicals out of protein rest streams, with opportunities to close the carbon and nitrogen cycle.

((Insert TOC Graphic here))

*Dr. Free De Schouwer, Dr. Laurens Claes, Annelies Vandekerkhove, Dr. Jasper Verduyckt, Prof. Dirk E. De Vos**

Page No. – Page No.

Protein-rich biomass waste as a resource for future bio-refineries: state of the art, challenges and opportunities

Layout 2:

REVIEW

((Insert TOC Graphic here))

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Text for Table of Contents