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'Green' synthesis of amines from renewable resources? A detailed analysis of case studies using the CHEM21 green metrics toolkit

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'Green' synthesis of amines from renewable resources? A detailed analysis of case studies using the CHEM21 green metrics toolkit†

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Amines play pivotal roles in both chemical industry processes and various biological functions, necessitating efficient and sustainable synthesis methodologies. Despite the emergence of greener catalytic methods in the past decades, assessing the environmental impact of these processes remains a challenge. While bio-based amine synthesis from renewable sources appears inherently green, comprehensive evaluation across diverse sustainability metrics is imperative. This tutorial review explores the methodology of such assessments, focusing on the systematic evaluation of amine synthesis pathways using the CHEM21 green metrics toolkit. Targeting early career researchers, we provide a step-by-step demonstration to integrate this toolkit into laboratory practices, empowering researchers to evaluate the environmental footprint of their chemical transformations. By promoting the use of green metrics, we aim to foster a greater understanding of sustainability in chemical research and encourage environmentally conscious decision-making.

Green foundation

1. Amine-containing compounds find application in various fields ranging from pharmaceuticals, polymers, surfactants and detergents, just to name a few. In this tutorial review, we show the sustainable production of these compounds *via* hydrogen borrowing, reductive amination and hydroamination, directly from renewable resources. We further evaluate the greenness and sustainability of these processes using the CHEM21 green metrics toolkit.

2. Shifting to sustainable synthetic methods is becoming more and more important. To facilitate this shift, this review will help early-career researchers to incorporate this toolkit into laboratory practices. It also provides a basic evaluation of the feasibility of incorporating renewable resources into the synthesis of value-added chemicals.

3. As the availability of renewable resources on a large scale grows, these synthetic and catalytic methods have the potential to substitute the current petrochemical routes. However, further insights regarding their environmental impact are necessary, and this review provides a first glimpse into the effectiveness and sustainability of these approaches.

1. Introduction

Nitrogen-containing compounds play a central role in all fields of chemistry; among them, amine and amide derivatives (nucleotides and amino acids) are the most fundamental building blocks that Nature has chosen in the construction of Life.[1,2] Besides biochemistry, amines are centrally important compounds in the bulk and fine chemical industry since they are omnipresent scaffolds in agrochemicals, dyes, natural products, pharmaceutically active compounds, and polymers.[3,4] The vast majority of these products originate from depleting fossil resources and are frequently manufactured through environmentally unfriendly routes, multistep syntheses, and generating large amounts of waste.[5,6] A change of unsustainable practices is highly desired: we should be able to obtain the needed chemicals from renewable resources, through clean catalytic routes, without generating large amounts of waste. Lignocellulosic biomass and derived platform chemicals are highly oxygenated, hence ideally positioned for the development of such zero-waste, catalytic pathways.

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Terrestrial biomass, a complex natural renewable material, has a potent carbon-capture capability (est. 200 Gt at 4.4×10^9 ha canopy cover potential),[7] combined with enormous chemical variability. Unlike fossil fuels, biomass is replenished in time, which makes it a promising alternative feedstock for the sustainable production of chemicals. While the structural complexity of biomass represents challenges in terms of processing and conversion/depolymerization,[8] it also offers unique possibilities for developing entirely new, energy-efficient, and waste-free pathways to obtain valuable chemicals.[9,10] Recently, specific effort has been devoted to the development of strategies for the synthesis of amines from renewables *via* waste-minimized catalytic routes.[9–11] The main objective of this review is to summarize recent progress and guide the readers through the evaluation of these developments in a green chemistry context.

Amines are highly important and their synthesis is well established in the chemical industry. Classical synthetic methods to access amines include the Gabriel synthesis of alkyl halides[12] and reductive alkylation processes.[13] However, these approaches suffer from low atom economy due to the formation of stoichiometric amounts of waste, low selectivity, and encounter some restrictions in substrate cost and availability. Catalytic methods such as Buchwald–Hartwig,[14,15] Ullmann reactions[16,17] have emerged to be efficient and powerful alternatives, albeit these methods typically utilize halides as substrates, which negatively affects atom economy and are not readily applicable to the conversion of renewable platform chemicals.

Biomass and derived platform chemicals contain specific functional groups (alcohols, aldehydes, acids) that represent valuable precursors, easing the synthetic pathways and potentially reducing the number of steps needed for synthesizing targeted products.[18,19] With regard to the mission of developing efficient catalytic pathways from biomass without the formation of side products, several catalytic methods can be envisioned. These approaches, which have – independently of biomass conversion – gained intensive interest due to their sustainability, are (i) 'hydrogen borrowing' amination of alcohols;[20–23] (ii) reductive amination of aldehydes and ketones;[24–26] (iii) hydroamination of unsaturated alkanes.[27–29] In this review, all three research areas will be thoroughly discussed.

But how to properly evaluate the 'greenness' of a chemical reaction and process? This is a non-trivial question, which has been engaging the 'green chemistry' community over the past decades. The 12 principles of Green Chemistry are a set of design guidelines, established to facilitate the fundamental discovery process, where holistic 'green chemistry' thinking rests at the core of the research questions, prioritizing pollution prevention and the development of clean transformations. There are specific green metrics (as detailed below) describing a chemical reaction, which are directly connected to the principles of Green Chemistry. These are related to the amount of waste generated (*E* factor, 1st principle) or the percentage of atoms incorporated in the final products (atom economy, 2nd principle). Calculation of these relatively simple numerical values is therefore an important first step of evaluation, yet not entirely comprehensive without a full life-cycle analysis. In this tutorial review, we will show the application of these metrics to specific transformations. To take this further, more comprehensive evaluation methods have been developed, taking into account a broader set of parameters and specific aspects of the entire process. For example, the CHEM21 green metrics toolkit, developed by Clark and co-workers,[30] was introduced to provide a practical and relatively easy-to-use tool for objective evaluation and quantification of a process, aligning with the Twelve Principles of green chemistry. This method incorporates resource efficiency (waste, atom economy, energy), environmental, health, and safety considerations of the reaction and related purification protocols.[31] Thus, the CHEM21 green metrics toolkit assists in the calculation and assessment of key quantitative and qualitative parameters, giving a suitable starting point for reaction development. Subsequently, it is desired to perform a full life cycle analysis (LCA), including feedstock sourcing and product end-of-life considerations, to derive final conclusions about the environmental impact and feasibility of a process.[32,33] Since LCA is resource and time-intensive and requires specialized knowledge, it typically cannot be routinely performed in every laboratory. Therefore, the main focus of this review is devoted to the calculation of metrics and the use of the CHEM21 toolkit, which can be easily performed in any laboratory by students and post-doctoral researchers.

The goals of this tutorial review are multifold. First, we give an overview of the types and classes of renewable starting materials and platform chemicals, which can be used to produce bio-based amines. Next, we discuss three specific types of catalytic reactions, namely (i) catalytic *N*-alkylation of amines with alcohols *via* 'hydrogen borrowing' methodology, (ii) reductive amination, (iii) hydroamination, including recent developments in catalyst development in these domains (Fig. 1). The attention will be focused on heterogenous and homogenous metal catalysts. Then we demonstrate the use of these catalytic transformations for the development of specific bio-based amines on selected examples. And finally, we demonstrate the use of green metrics and the CHEM21 green metrics toolkit for evaluating selected reactions. These calculations will reflect upon the combination of mild biomass depolymerization and clean amination strategies towards the sustainable synthesis of amines from renewables, compared to petroleum.

2. Green metrics

The prime goal of green chemistry is to minimize the formation of waste in the design and manufacturing of chemical processes and products.[18] Over the past years, metrics for measuring/quantifying the green credentials of a process, such as atom-economy (AE), reaction mass efficiency (RME), process mass intensity (PMI) were introduced. The list of green metrics will be discussed in detail in this chapter.[34] Green metrics

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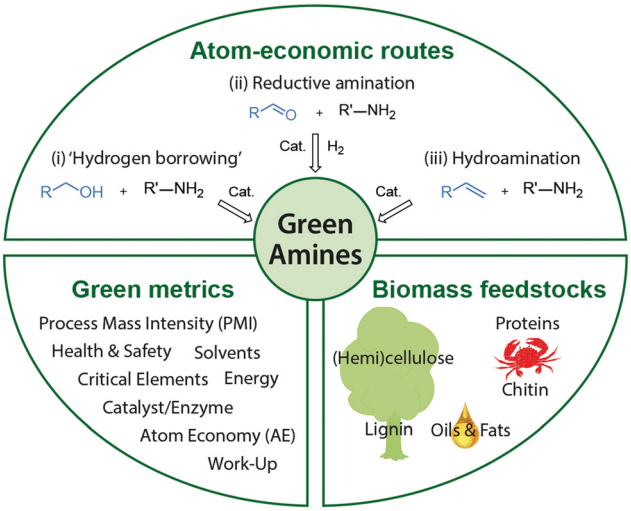

Fig. 1 Overview of the present review: synthesis of green amines starting from renewable resources using atom-economic transformations following the principles of green chemistry.

should be used to calculate improvements in the greenness of new synthetic pathways by comparing them to current methodologies.

As earlier mentioned, the CHEM21 green metrics toolkit[35] serves as a practical guide for the evaluation of chemical processes from a green chemistry perspective. Considering the researcher's goals, the toolkit is divided into four passes, from zero pass to third pass, with different parameters included in each. While the zero and first pass toolkits are designed to be used on a bench scale, the second and third pass ones are to be employed on an industrial level. Reactions that were shown to be promising on the zero and first pass are subjected to more in-depth analysis studying their scalability, therefore life cycle assessment (LCA) is not incorporated until the second pass CHEM21 metrics toolkit. The reason behind such a structure of passes with a level of complexity corresponding to the scale of the experiment is that the system of green metrics should primarily give a meaningful assessment, being simple to utilize in everyday laboratory practice.

In this chapter, we will detail green metrics that are calculated using the first pass CHEM21 metrics toolkit to provide a preliminary assessment of new reactions performed on the laboratory scale, at the discovery level. In the following chapters, we are going to use these parameters to evaluate the greenness of selected catalytic reactions and identify the potential areas for improvement.

2.1 Quantitative parameters

The basic parameters that describe a chemical transformation are yield, conversion, and selectivity. The equations for calculating these parameters are presented in Fig. 2, from a green chemistry point of view, a reaction with high yield, conversion, and selectivity is highly desirable. Here it is worth clarifying the difference between a reactant and a reagent since we will operate with these terms further. A reactant is defined as a compound containing at least one atom that is incorporated into the final product, while a reagent is a compound that is consumed during the reaction but not included in the product.

With the help of such metrics as atom economy (AE)[36] and reaction mass efficiency (RME), chemists gain insight into the extent to which the reactants are converted into the target product (Fig. 2). AE is calculated as the ratio of the molecular weight of the product to the sum of the molecular weights of all reactants. Notably, AE, being a fully theoretical parameter, inherent to the reaction and does not incorporate the excesses of the used reactants. The latter drawback is successfully implemented in the RME.

In contrast to the mass-based metrics mentioned above, the process mass intensity (PMI), defined as "the mass of all chemicals used in the reaction divided by the mass of the isolated product", includes all mass-based inputs: yield, stoichiometry, solvents, reagents, and work-up (Fig. 2). Later in this review, this parameter will be divided into three categories in order to simplify its assessment. As such, PMI reactants, reagents and catalysts (PMI RRC), which includes, as it is named, reactants, reagents, and catalysts; PMI reaction (PMI Rxn), besides the mentioned parameters involves reaction solvents; PMI work-up (PMI WU) considers only the auxiliary materials and solvents for the work-up. Recently, new metrics such as feedstock intensity (FI) and circular process feedstock intensity (CPFI) were developed.[37] Being calculated in a similar way as PMI, these parameters are taken into account besides the desired product formation the production of valuable co-products (FI) as well as recycling of the material (CPFI). However, in this tutorial review, we will not implement these additional parameters in our analysis.

2.2 Qualitative parameters

At the First Pass level, the quantitative parameters such as mass-based metrics are calculated, and the obtained numerical values are compared, while qualitative metrics such as solvent, energy consumption, environmental concerns, are measured with a color code. This way, the results are flagged green (preferred), yellow (acceptable, but with some issues), and red (undesirable), indicating how well that parameter fits into the green and sustainable scoring system and/or pointing to an issue associated with the certain parameter. The following is a brief overview of qualitative parameters to be considered in a green metrics analysis at the first pass level.

The use of stoichiometric or superstoichiometric amounts of reagents instead of using a catalyst/enzyme receives yellow or red flags, respectively. The possibility to regenerate and reuse the catalyst is scored with a green flag. The presence of critical elements[38] with the risk of depletion of less than 50 years is marked in red, in a time interval between 50 and 100 years – yellow, and more than 100 years – green flag. This is interesting to keep in mind – even though a reaction is catalytic which is desired by the 9th principle of Green Chemistry, the use of rare metals for these processes, especially without appropriate recycling, markedly impacts the sustainability of the developed approach. The work-up method is evaluated by assigning a

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Fig. 2 Overview of the first pass CHEM21 green metrics toolkit: quantitative (inner circle) and qualitative parameters (outer circle). Abbreviations: R – reactant; R_l – limiting reactant; P – product; n_P – moles of product formed; $n_{i,\,R_l}$ – initial moles of limiting reactant; $n_{f,\,R_l}$ – moles of limiting reactant left; m – mass; M_w – molecular weight.

green flag to procedures with lower solvent consumption such as evaporation, filtration, centrifugation; in this case, column chromatography commonly used in organic synthesis receives a red flag. The same idea underlies the choice of batch or flow set-up: less solvent and energy-consuming flow set-up is marked with a green flag, the batch one – with a yellow flag.

The assessment of the energy use is significantly simplified for the discovery phase (first pass level) and considers the absolute temperature of the reaction: between 0 °C and 70 °C receives a green flag, lower than −20 °C or higher than 140 °C – red flag, and intermediate values – yellow flag. Furthermore, the reaction temperature is compared with the boiling point of the reaction solvent used, obtaining a red flag if the reaction is carried out under the reflux conditions. On the contrary, a green flag is assigned to a reaction whose temperature is lower than the boiling point of the solvent by 5 °C or more.

To evaluate potential health and safety concerns, the respective MSDS files of all chemicals involved in a reaction

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should be analysed. In this case, the colour code depends on how hazardous the used materials are and is assigned with red, yellow, and green flags, respectively. The open-access CHEM21 Solvent Selection guide, based on the solvent's physical properties, peroxability, resistivity, possible impact on the environment, and health, should be considered for scoring the utilized solvents.[39]

3. Catalytic approaches for the synthesis of bio-based amines

3.1 *N*-Alkylation of amines with alcohols *via* the 'hydrogen borrowing' strategy

3.1.1 General considerations. The *N*-alkylation of amines with alcohols *via* the 'borrowing hydrogen' approach (also called 'hydrogen auto-transfer') has emerged as one of the most attractive and waste-free alternatives to provide *N*-alkylated amines.[40]

This atom-economic transformation represents a prime example in green chemistry since it only produces water as a by-product and does not require any additional external hydrogen source since the parent alcohol acts as a hydrogen donor. Moreover, this methodology utilizes widely available inexpensive alcohol reaction partners that can be potentially derived from renewable resources.[41–43] More specifically, the 'hydrogen borrowing' strategy begins with the metal-catalysed dehydrogenation of the alcohol substrate. Further, the formed carbonyl compound reacts with the amine to form the corresponding imine, which is reduced to the alkylated amine by means of the metal hydride generated during the first dehydrogenation step (Fig. 3).[40] It is no surprise therefore, that the development of an appropriate catalytic species able to efficiently catalyse both the dehydrogenation and imine reduction steps, is key to achieving desired efficiency and selectivity in the overall transformation.

In 1981, Watanabe[44] and Grigg[45] reported the first homogeneous catalysts, namely iridium, rhodium, and ruthenium-based phosphine complexes, for the *N*-alkylation of amines with alcohols (Fig. 4). Following these pioneering works after three decades of discovery, Fujita[46] disclosed an efficient catalytic system consisting of $[Cp^*IrCl_2]_2/K_2CO_3$ (Cp^* = pentamethylcyclopentadienyl) for the selective mono-alkylation of primary amines to produce secondary amines. With regard to ruthenium, Beller's[47] and Williams's[48] groups reported on the use of $Ru_3(CO)_{12}$ with bulky phosphines and $[Ru(p\text{-cymene})Cl_2]_2$ with the bidentate phosphines dppf or DPEphos as the catalyst, respectively, capable of alkylating amines with alcohols. The latter catalyst system has proven its efficiency for the synthesis of some simple pharmaceuticals, as well as for cyclization reactions and the *N*-alkylation of sulfonamides. While a large number of protocols have been developed in this field using precious metals[20,49,50] for *N*-alkylation of amines with

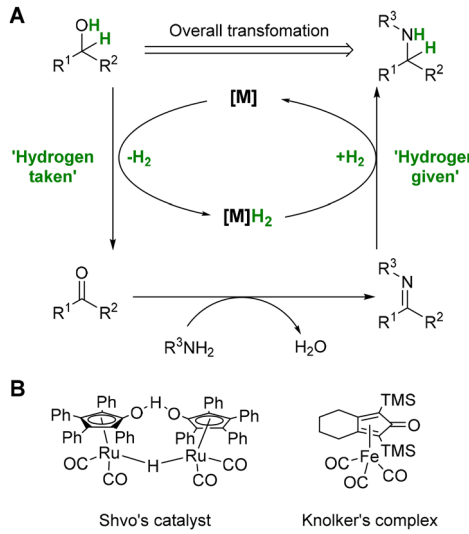

Fig. 3 (A) General mechanism of the hydrogen borrowing strategy; (B) Shvo's catalyst and Knölker's complex.

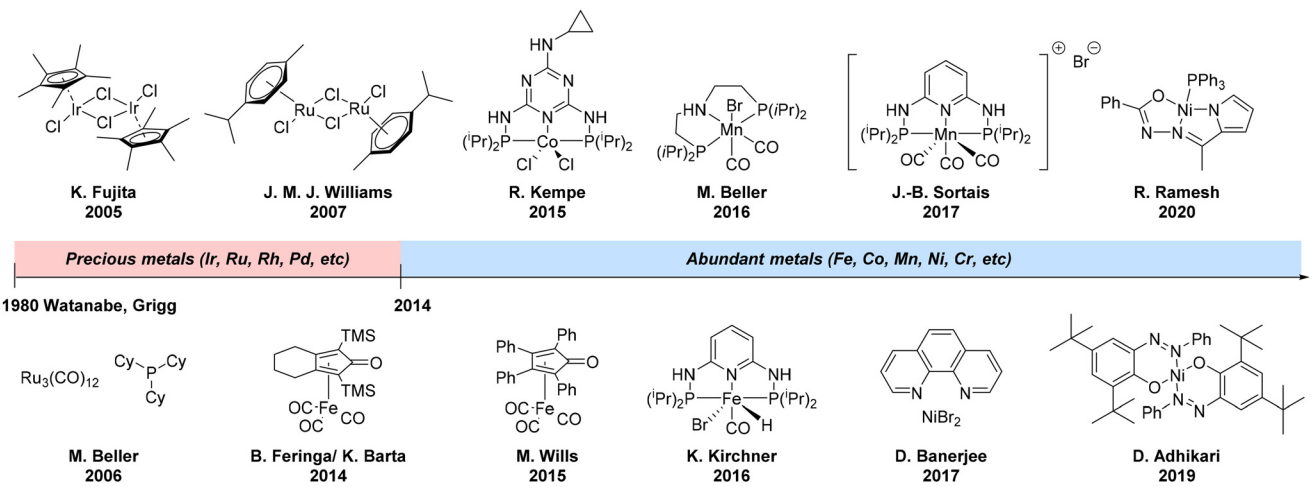

Fig. 4 *N*-Alkylation of amines with alcohols using the 'hydrogen borrowing' strategy: history and key milestones.

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alcohols, since 2014 there have been more reports about the use of base metal catalysts for this transformation. Thus, almost simultaneously, Feringa and Barta with the Wills group demonstrated the C–N bond formation between alcohols and amines using iron-based homogeneous Knölker's complex[51] and iron-tetraphenylcyclopentadienone tricarbonyl complex,[52] respectively. Later, Kirchner and co-workers reported the use of complexes [Fe(PNP)Br_2] and [Fe(PNP)(CO)Br_2] comprising PNP pincer ligands based on triazine and pyridine backbones for the same type of transformation.[53]

Besides iron and cobalt,[54,55] manganese pincer[56,57] complexes were successfully applied for the selective *N*-alkylation of amines with alcohols. Remarkably, as reported by Beller,[58] manganese-based catalytic protocol allowed the *N*-methylation of various amines with methanol, which constituted the first examples of this transformation using non-noble metal complexes under mild reaction conditions. The first homogeneous nickel-based catalyst systems as a combination of nickel bromide and 1,10-phenanthroline and a well-defined and bench-stable azo-phenolate ligand-coordinated nickel catalyst capable of *N*-alkylation of a variety of anilines with alcohols were described by Banerjee[59] and Adhikari[60] groups, respectively. Soon after, efficient protocols emerged using Ni(II) pincer-type complex[61] and nickel nanoparticles[62] for the same type of reaction. Recently, the major focus of the field has shifted towards the asymmetric version of amination *via* the 'hydrogen borrowing' strategy.[63] Thus, Donohoe group disclosed an elegant iridium-catalysed annulation strategy for the stereo-controlled synthesis of substituted saturated azaheterocycles as well as the synthesis of enantioenriched C3-substituted pyrrolidines and piperidines from enantiopure 1,4- and 1,5-diols.[64]

The recent breakthroughs in the usage of earth-abundant metals in homogeneous 'hydrogen borrowing' catalysis have been extensively reviewed.[21–23,65] However, despite the achievements in the field, there is still tremendous demand for novel methods using precious or non-precious metals with improved scope, higher stability, higher TON, and applicability to bio-derived substrates.

Nonetheless, the literature offers several cases where hydrogen borrowing was utilized for Kg-scale pharmaceutical synthesis. For example, in 2011 Pfizer developed the $[Cp^*IrCl_2]_2$ catalysed synthesis of a GlyT1 Inhibitor by using a hydrogen borrowing reaction as the key step.[66] The optimized alcohol amination step allowed to improve the step economy, enabling the use of a catalyst loading as low as 0.05 mol% while resulting in the isolation of 4.81 kg of the amine product (76% yield). Similarly, Gonzales-Bobes from Bristol Myers Squibb recently reported the 2.8 kg synthesis (>70% yield) of an *N*-alkylated pyridine-2-amine *via* Ir-catalysed hydrogen borrowing.[67] Although these reports do not involve the use of biomass-derived precursors, they underscore the increasing use of this attractive approach to minimize the economic and environmental impact of industrially relevant amines synthesis.

3.1.2 Biomass-derived precursors for the synthesis of bio-based amines by hydrogen borrowing. Alcohol and amine functionalities are ubiquitous in biomass, making them highly desired substrates in amination or *N*-alkylation reactions *via* the 'hydrogen borrowing' methodology.

Taking into account that biomass is a complex natural renewable material with enormous chemical variability, hereinafter each type of biomass as a potential precursor for amines synthesis is separately described. Due to the large number of reports on the amination of bio-based alcohols in recent years, only selected examples have been discussed in this tutorial review (for more examples and details, see the recent review on this topic[68]).

Carbohydrate derivatives. Lignocellulosic biomass is a robust complex biopolymer that is primarily composed of cellulose, hemicellulose, and the aromatic polymer lignin. (Hemi)cellulosic carbohydrates are the largest fraction of lignocellulose; processes for the production of a number of platform chemicals by chemo- or biocatalytic methods are well-established.[89] Some of these chemicals are termed 'top value-added platform chemicals from carbohydrates'.[90] Among these, there are several examples that feature an alcohol or carbonyl moiety. Herein the conversion of (hemi)cellulose-derived alcohols into amines *via* the 'hydrogen borrowing' approach is discussed (Table 1).

Alcohols are important building blocks, inherently contained in and readily sourced from biomass. Perhaps the most simple and prominent primary alcohol, typically derived from syngas originating from thermal biomass conversion methods, is methanol.[91] The other important short-chain alcohol, ethanol, could be obtained from cellulose *via* the fermentation of glucose.[92] Furthermore, ethylene glycol can be subsequently obtained by dehydration of ethanol to ethene followed by conventional routes or alternatively by sugar or sorbitol/polyols hydrogenolysis pathways.[91] Several methods have been developed for the conversion of cellulose-derived 5-(hydroxymethyl) furfural (5-HMF) or hemicellulose-derived furfural into various diols such as 1,6-hexanediol, 1,4-butanediol.[93] On the other hand, the hydrogenation of glucose results in the formation of sorbitol.[94]

Direct amination of short-chain alcohols such as methanol, ethanol, propanol as well as diols is a well-established fundamental process producing alkylated amines that are highly essential in the chemical industry.[95] Myriads of heterogeneous catalyst systems are known to carry out such transformation, therefore herein we will mention only selected ones. Baiker[96] reported the gas phase amination of ethylene glycol (EG), potentially produced from cellulose, with dimethylamine (DMA) in a continuous fixed-bed reactor at atmospheric pressure over an Al_2O_3-supported Cu catalyst allowing the selective production of both ethanolamine, an important building block for detergents,[97] and ethylenediamine, a common bidentate ligand in organometallic catalysts,[98] products. The same group later discovered the Co–Fe system for the amination of 1,3-propanediol with supercritical ammonia.[99] Other heterogeneous catalytic systems for the amination of aliphatic bio-derived diols, namely 1,2-propanediol, 1,4-butanediol, and 1,6-hexanediol have been described

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Table 1 Sustainable amination of (hemi)cellulose- and lignin-derived alcohols *via* 'hydrogen borrowing' methodology

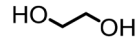
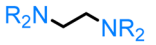
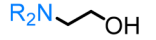
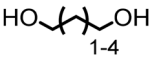
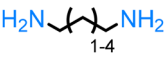
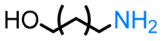
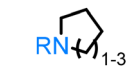
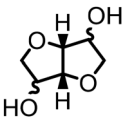
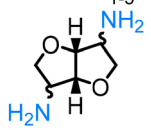
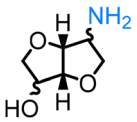
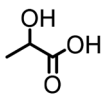
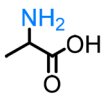
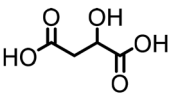
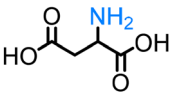
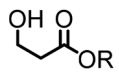
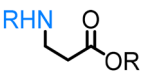
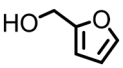
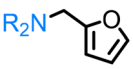
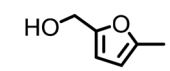
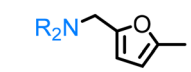
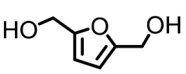
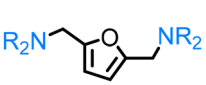
Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
(Hemi) cellulose		$[IrH_2Cl\{(iPr_2PC_2H_4)_2NH\}]$, amine, 140 °C, 20 hr		0.062 g–0.090 g (1 mmol)	1 mmol	C2–C4: 77–97%	69
		$[Cp^*IrCl_2(bmim)]$, K_2CO_3, toluene or $N_{1,8,8,8}NTf_2$, 115 °C, 24–48 hr		0.152 g (2 mmol)	2 mmol	C3: 89–99%	70
		Knölker cat., Me_3NO, CPME, 130 °C, 18–44 hr		0.090 g–0.118 g (1 mmol)	0.5 mmol	C4–C6: 60–85%	51
							
							
		Ru/C, aq ammonia, 10 bar H_2, 170 °C, 6 hr		1 g (6.84 mmol)	6.84 mmol	45%	71
		$[Ru(CO)ClH(PPh_3)_3]$/Xantphos, ammonia, *t*-amyl alcohol, 170 °C, 20 hr		0.146 g (1 mmol)	1 mmol	96%	72
		$[Ru_3(CO)_{12}]$, A-iPr-PNP, aq ammonia, *tert*-amyl alcohol, 170 °C, 21 hr		1.461 g (10 mmol)	10 mmol	96%	73
		Ni/Al_2O_3-SiO_2, aq ammonia, *t*-amyl alcohol, 160 °C, 18 hr		0.073 g (0.5 mmol)	0.5 mmol	51%	74
		[Ir] cat., $(HO)P(O)(OPh)_2$, toluene, 3 Å mol. sieves, 120 °C, 24 hr		0.060 g–0.080 g (0.25–0.5 mmol)	0.25–0.5 mmol	11–83%	75 and 76
		Ru/CNT, aq ammonia, 10 bar H_2, 220 °C, 2 hr		0.045 g–0.067 g (0.5 mmol)	0.5 mmol	62% 27%	77
							
	 R = Et, tBu	Shvo cat., DPP, amine, toluene, 120 °C, 18 hr		0.118 g–0.146 g (1 mmol)	0.5 mmol	45–72%	78
		Nanosized zeolite Beta, aniline, 135 °C, 4 hr		0.589 g (6 mmol)	2 mmol	52%	79
		$RuCl_3$ $3H_2O$, dppf, amine, PhCl, 145 °C, 15 hr		0.059 g (0.6 mmol)	0.2 mmol	68%	80
		$[Ru_3(CO)_{12}]$, CataCXium PCy, ammonia, 150 °C, 20 hr		0.098 g (1 mmol)	1 mmol	71%	81
		[RuHCl(A-iPr-PNP)(CO)], ammonia, toluene, 110 °C, 12 hr		0.981 g (10 mmol)	10 mmol	95%	82
		$[Mn(iPr_2PC_2H_4)_2NH)(CO)_2Br]$, *t*-BuOK, amine, toluene, 80 °C, 24 hr		0.118 g (1.2 mmol)	1 mmol	37–51%	56
		Ni/Al_2O_3-SiO_2, aq ammonia, *t*-amyl alcohol, 160 °C, 18 hr		0.049 g (0.5 mmol)	0.5 mmol	52%	74
		Knölker cat., Me_3NO, amine, toluene, mol. sieves, 135 °C, 18–24 hr		0.224 g–0.256 g (2 mmol)	0.5 mmol	59–60%	83
		[RuHCl(A-iPr-PNP)(CO)], ammonia, *t*-amyl alcohol, 150 °C, 7 hr		0.640 g (5 mmol)	5 mmol	65%	84
		Ru-20MgO/TiO_2, ammonia, toluene, 110 °C, 20 hr		0.064 g (0.5 mmol)	0.5 mmol	86%	85

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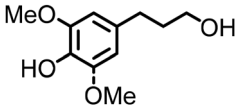
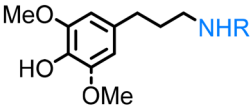
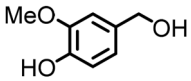
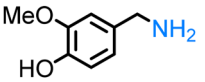
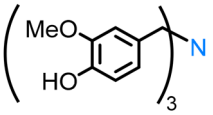
Table 1 *(Contd.)*

Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
Lignin		Shvo catalyst, amine, CPME, 130 °C, 20 hr		0.087 g–0.102 g (0.48 mmol)	0.4 mmol	43–98%	11
		RANEY® Ni, ammonia gas, *t*-amyl alcohol, 160–180 °C, 18 hr		0.091 g–0.106 g (0.5 mmol)	0.5 mmol	65–76%	86
		Cu-SiO_2, DMAn, 3 bar H_2, *o*-xylene, 210 °C, 16 hr		0.182 g–0.212 g (1 mmol)	1 mmol	83–84%	87
		Ni/Al_2O_3-SiO_2, $(NH_4)_2CO_3$, *t*-amyl alcohol, 140 °C, 18 hr		0.077 g (0.5 mmol)	0.5 mmol	40%	74
		Au/TiO_2-VS, urea, toluene, 140 °C, 5 bar N_2, 18 hr		0.092 g (0.6 mmol)	0.1 mmol	80%	88

as well.[100] Some selected homogeneous catalyst systems, namely *N*-heterocyclic carbene iridium complex,[70] as well as iridium pincer metal species,[69] were found to be efficient for the amination of short aliphatic chain alcohols and diols. Remarkably, Knölker's complex was successfully applied for the amination of diols furnishing the formation of various saturated azaheterocycles.[51]

Another essential type of diols is dianhydrohexitols, which could be obtained by double dehydration of the corresponding hexitols. Rose[71] developed selective mono- and diamination of isosorbide, in the presence of a Ru/C catalyst; the obtained products could be used as polymer building blocks in polyamide[101] and polyimide[102] synthesis. Our group has reported the synthesis of the mono-aminated isosorbide product using Ni/Al_2O_3-SiO_2 as a catalyst.[74] Besides the mentioned heterogeneous catalysts, Beller reported the amination of isosorbide with ammonia using commercially available [Ru(CO)ClH(PPh_3)$_3$]/Xantphos catalyst.[72] Similar example of a Ru-based catalytic system was described by Vogt.[73] Interestingly, this robust catalytic system could be applied for the amination of natural alcohols as well, such as nerol, geraniol, farnesol, apart from the diols. Stereoselective aminations of partially protected isohexides, namely *exo*-monobenzylated isosorbides,[75] as well as unprotected ones[76] were established by Popowycz and co-workers applying Ir-based catalyst system along with diphenyl phosphate as an additive.

Multiple examples of conversion of hemicellulose-derived furfuryl alcohol to the corresponding furfuryl amine are established over heterogeneous catalysts (nanosized zeolite beta,[79] Ni/Al_2O_3-SiO_2,[74] Ru-20MgO/TiO_2,[85] Ru nanoparticles[103] *etc.*). Among known homogeneous systems, Milstein disclosed the selective synthesis of furfuryl amine directly from furfuryl alcohol and ammonia in the presence of acridine-based pincer complex [RuHCl(A-iPr-PNP)(CO)].[82] Following this study, other ruthenium-based catalyst systems for the direct amination of alcohols, including bio-based furfuryl alcohol, with aliphatic tertiary amines[80] and with ammonia[81] were developed. A few examples of the amination of furfuryl alcohol in the presence of manganese pincer complexes under strikingly mild reaction conditions were demonstrated by Beller.[56]

Regarding the cellulose-derived 5-HMF, it could also serve as a starting material for the construction of bio-based amines. Our group reported the highly selective hydrogenation of 5-HMF to 2,5-furan-dimethanol using Cu/Zn alloy nanopowder[104] and Cu20-PMO catalysts[105] under mild conditions (up to 100 °C) and the subsequent selective amination of the obtained diol using Knölker's complex.[83] One homogeneous[84] and one heterogeneous[85] catalyst system is known in the literature for the synthesis of 2,5-bis(aminomethyl)furan (BAMF) using ammonia as a nitrogen source.

α-Hydroxy acids (*e.g.* lactic acid, malic acid) are important, primary platform chemicals readily accessible from renewable carbohydrates and, notably, several examples belong to the Top 12 value-added biomass-derived platform chemicals.[90] To the best of our knowledge, the direct amination of α-hydroxy acids remains a rarity. Yan reported the first example of the amination of lactic acid with ammonia catalysed by a heterogeneous ruthenium-based catalyst.[77,106] This pioneering work represents an alternative, chemocatalytic approach for the synthesis of amino acids, enabling for the first time the production of valuable proteins from lignocellulosic biomass. Our group has developed a homogeneous catalyst system based on a combination of Shvo's catalyst and Brønsted acid additive for the amination of 3-hydroxypropionic acid esters (3-HPe) *via* the 'hydrogen borrowing' strategy.[78] This work demonstrates a very important pathway for easy access to beta-amino acid scaffolds from biomass.

Lignin derivatives. Lignin is the largest source of bio-renewable aromatics. Its chemical structure consists of phenylpropane units, originating from three aromatic alcohols: *p*-coumaryl, coniferyl, and sinapyl alcohol, and therefore it is a promising feedstock for producing bio-aromatic alcohols and further functionalized derivatives. It is worth mentioning that before the recent work of our group[11] there were no reports on the direct synthesis of amines from lignin-derived monomers by the 'borrowing hydrogen' method: reported protocols

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focused on lignin oligomers or reductive amination of vanillin.[43] The reason for limited studies on lignin monomers was the limited availability of lignin-derived platform chemicals due to the recurrent depolymerization challenge.

Lignin oxidation is a classical way of lignin depolymerization, though also associated with lower monomer yields.[107] Recently, methods that deliver higher yields of vanillin or syringaldehyde have been developed,[108] therefore, the hydrogenation of these building blocks to the corresponding alcohols (and their subsequent amination) becomes a feasible alternative. Indeed, there are few reports of applying 'hydrogen borrowing' methodologies to vanillyl alcohol, syringyl alcohol, or even the simpler *p*-hydroxybenzyl alcohol as a substrate (Table 1). Cao reported an example of the direct synthesis of tertiary amine from vanillyl alcohol and urea in the presence of the heterogeneous gold-mediated system.[88] Our group demonstrated the direct amination of vanillyl alcohol using Ni/Al_2O_3-SiO_2 as a catalyst and $(NH_4)_2CO_3$ as an ammonia source.[74] Furthermore, we developed a RANEY® Ni-based amination methodology (with ammonia) capable of converting lignin-derived phenolic primary alcohols, such as dihydroconiferyl alcohol, to corresponding primary amines.[86]

The introduction of the concept of stabilization of reactive intermediates[109] during lignin depolymerization, the so-called 'lignin first' strategies[110] have significantly shaped the possibilities to suppress undesired recondensation phenomena and obtain monophenolic compounds, for example, propyl- or ethyl-guaiacol and syringol or propanol-guaiacol or syringol in high yield from organosolv lignin or lignocellulose.[108] These compounds may become potential platform chemicals in the future. It was shown in the recent works of our group, that employing homogeneous Shvo's catalyst leads to the first example of catalytic amination of lignin-derived dihydroconiferyl and dihydrosinapyl alcohols[11] demonstrating the feasibility of this complex for the synthesis of *N*-alkyl aminophenols. Our group also reported a catalytic strategy for producing industrially relevant 4,4′-methylenebiscyclohexamine from lignin oxidation mixtures in two steps; this occurs *via* the catalytic funneling of lignin-derived bisphenol mixtures into 4,4′-methylenebiscyclohexanol (MBC) and direct amination of MBC with ammonia.[111] Efficient Cu-catalysed hydrogen borrowing strategy was developed by Sels and co-workers to functionalize aliphatic alcohols in aromatic monomers and dimers, derived from lignin by the reductive catalytic fraction (RCF), into tertiary dimethylamines.[87] Very recently, Yan disclosed an elegant single-step catalytic strategy for directly producing phenolic amines from wood lignin *via* RCF in an aqueous ammonia–alcohol mixture over Ru catalyst.[112] Remarkably, all amine products obtained through the above-mentioned strategies can be further upgraded into products with enhanced functions, thereby increasing the economic feasibility of lignocellulosic biorefineries.

Triglycerides. Oils and fats, chemically composed of mainly triglycerides, are plant-based, and typically used for the food industry. Recently, large amounts of waste cooking oils are generated composed of specific triglycerides, which should find better utilization as a renewable feedstock for the chemical industry. Triglycerides are esters of glycerol composed of various linear saturated or unsaturated long–chain carboxylic acids (C8–C22). The most prominent and larger-scale application of triglycerides is the production of fatty acid methyl esters (FAME) by transesterification with methanol, leaving glycerol as a by-product in significant quantities. Both glycerol, as well as FAME or the derived fatty alcohols (FAO), obtained upon hydrogenation of FAME[113] have been investigated as renewable starting materials to produce a range of bio-based products.[114]

The amination of fatty alcohols (Table 2) with dimethylamine is one of the main commercial processes for the production of dimethylalkylamines, and one of the key reactions for the oleo and detergents industries.[115] Employing various heterogeneous catalysts (Cu–Ni,[116] Cu–Cr,[117] Cu–Ni–Ba[118]) this reaction was extensively studied. Apart from the mentioned examples, there are multiple efficient heterogeneous catalyst systems known for the amination of long-chain aliphatic alcohols (some selected Ni[62,74,119,120] and Ru[121]-based catalyst systems are depicted in Table 2).

Significantly less homogeneous catalytic methods using long-chain aliphatic alcohols as coupling partners are reported.[54,56,59,122] Among them a suitable protocol was developed by our group – the *N*-alkylation of natural α-amino acids with long-chain fatty alcohols using Knölker's complex as a catalyst.[123] This methodology uses unprotected amino acids as coupling partners and discusses the possibility of the fully sustainable synthesis of surfactants entirely derived from biomass.

As mentioned above, glycerol – an unavoidable by-product of triglyceride transesterification or hydrolysis – is another important substrate in the field of biomass valorisation.[132] However, the presence of three hydroxyl groups in its structure causes considerable hurdles regarding the selective transformation of one single functional group. In the course of research on the amination of glycerol *via* the 'hydrogen borrowing' approach, BASF reported RANEY® Ni/RANEY® Co system[133] that allows selectively obtaining the 1,2,3-triaminopropane and 1,2-diamino-3-propanol as major reaction products. Crotti[125] established the first example of the formation of *N*-heterocyclic products using glycerol and *cis*- and *trans*-1,2-diaminocyclohexane as starting materials catalysed by the simple and versatile iridium derivative $[Cp^*IrCl_2]_2$ in water. Interestingly, the hydrogenated piperazines and benzimidazoles synthesised *via* this procedure are valuable building blocks to produce fine chemicals and pharmaceuticals. The direct amination of solketal, a 1,2-hydroxy-protected derivative of glycerol, *via* ruthenium-catalysed 'hydrogen borrowing' was extensively investigated by Kann.[124] The formation of the highly valuable prochiral aminoketones, the key intermediate for the synthesis of chiral amino alcohols, was demonstrated by Shi[126] over $CuNiAlO_x$ catalyst; the latter is formed *via* dehydration of glycerol followed by the amination of the hydroxyacetone intermediate.

Recently, an elegant protocol to convert 'waste' glycerol from the biodiesel industry *via* lactic acid to alanine in a single step over a Ru_1Ni_7/MgO catalyst was disclosed by Yan.[127]

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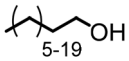
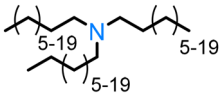
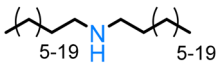
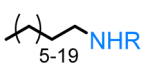
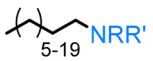
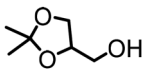
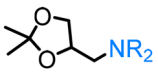
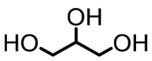
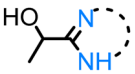
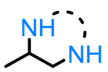
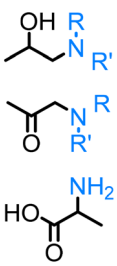
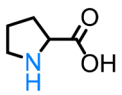
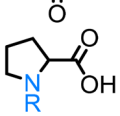
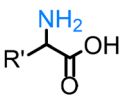
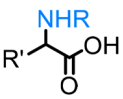
Table 2 Sustainable amination of bio-based alcohols and *N*-alkylation of α-amino acids *via* 'hydrogen borrowing' methodology

Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
Triglycerides		RANEY® Ni, aq ammonia, *t*-amyl alcohol, 180 °C, 18 hr		0.065 g–0.079 g (0.5 mmol)	0.5 mmol	C8–C10: 41–47%	74
		$Ni(COD)_2$, KOH, amine, CPME, 140 °C, 18 hr		0.195 g–0.406 g (1.5 mmol)	1 mmol	C8–C18: 85–90%	62
		$NiCuFeO_x$, amine, xylene, 140 °C, 24 hr		0.130 g–0.186 g (1 mmol)	1 mmol	C8–C12: 61–95%	119
		Ni/Al_2O_3, amine, *o*-xylene, 144 °C, 24 hr		0.156 g–0.190 g (1.2 mmol)	0.5–1 mmol	C8–C10: 88–99%	120
		$Ru(OH)_x/TiO_2$, urea, mesitylene, 1 atm Ar, 141 °C, 15 hr		0.326 g (2.5 mmol)	0.25 mmol	C8: 87%	121
		[Ru(CO)ClH(DPEphos)(PPh_3)], liq. ammonia, toluene, 140 °C, 24 hr		1.302 g (10 mmol)	10 mmol	C8: 71%	122
		Knölker-CH_3CN cat., amino acid, CF_3CH_2OH, 110 °C, 24 hr		0.827 g–0.830 g (5.2–6.3 mmol for C9-C10) 0.429 g–0.541 g (2 mmol for C14-C18)	0.5 mmol	C9–C18: 32–69%	123
		[$Mn(iPr_2PC_2H_4)_2NH$)$(CO)_2Br$], *t*-BuOK, amine, toluene, 80 °C, 24 hr		0.156 g (1.2 mmol)	1 mmol	C8: 85%	56
		[Co(TriazNHC$_3$H$_5$-iPr)Cl_2], *t*-BuOK, amine, toluene, 80 °C, 24 hr		0.327 g (1 mmol)	1 mmol	C22: 69–86%	54
		$NiBr_2$, 1,10-phenanthroline, *t*-BuOK, amine, toluene, 130 °C, 48 hr		0.145 g–0.198 g (1.25 mmol)	0.25 mmol	C7–C10: 59–76%	59
		[Ru(*p*-cymene)Cl_2]$_2$, DPEphos, amine, toluene or *tert*-amyl alcohol or neat, 130 °C, 48 hr		0.264 g (2 mmol)	2 mmol	52–92%	124
		[Cp*$IrCl_2$]$_2$, amine, base, H_2O or toluene or neat, 80–140 °C, 6–96 hr		0.100 g (1.1 mmol)	1.1 mmol	2–42%	125
		$CuNiAlO_x$, K_2CO_3, amine, 1,4-dioxane, 150 °C, 24–36 hr		0.460 g (5 mmol)	1 mmol	17–94%	126
		Ru_1Ni_7/MgO, NaOH, aq ammonia, 10 bar H_2, 220 °C, 4 hr		0.100 g (1.1 mmol)	1.1 mmol	Ala: 43%	127
Amino acids		Pd/C or $Pd(OH)_2$/C, alcohol, RT, 24–88 hr		0.1 mmol	0.1 mmol	*R*,*R*′: Alk 72–96%	128
		hν, Ag/TiO_2, alcohol, H_2O, 25 °C, 10 hr		2 mmol	2 mmol	94% (SM: L-Pro)	129
		Shvo or Knölker-CH_3CN cat., alcohol, 60–110 °C, 18–47 hr		0.2 mmol	0.2 mmol	*R*,*R*′: Alk 35–99%	123
		$Pd(OAc)_2$, TPPMS, alcohol, AcONa, H_2O, 120 °C, 16–24 hr		0.5 mmol	0.5 mmol	*R*,*R*′: Alk, Allyl 43–86%	130
		Ir(III)-NHC cat, alcohol, TFE, 90 °C, 20 hr		0.25 mmol	0.25 mmol	*R*,*R*′: Alk >95%	131

It was established that a multifunctional Ni-doped Ru catalyst system remarkably promoted the amination of lactic acid, the key intermediate of the reaction formed *via* sequential dehydrogenation, dehydration, and rearrangement. This methodology is capable of providing access to another class of valuable chemicals.

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Amino acids. Being a widespread class of nitrogen-containing compounds in nature, α-amino acids may serve as prominent sustainable alternatives to amines derived from petrochemicals *via* the energy-intensive Haber–Bosch process.[134] Remarkably, nature 'manufactures' amino acids with significantly less energy demand through the biocatalytic nitrogen fixation process.[135]

However, notwithstanding its abundance and availability the further functionalization of the natural amino acids, in our present case – the *N*-alkylation of the amino acids with alcohols *via* the 'hydrogen borrowing' approach – is a very challenging task. Firstly, most amino acids are pH sensitive and have limited solubility in non-polar organic solvents, a typical reaction medium for *N*-alkylation reactions. Secondly, competing esterification of the amino acid could take place instead of the desired *N*-alkylation. Thirdly, due to the addition of a strong base, typically required for most 'hydrogen borrowing' systems, the racemization of the substrate or the formed *N*-alkylated product could occur. Moreover, amino acid could potentially reduce the catalyst activity by means of coordination to the metal centre blocking the vacant coordination site essential for efficient catalysis.

To the best of our knowledge, in literature, there are few examples of direct *N*-alkylation of free amino acids with alcohols (Table 2) justifying the difficulty of such an approach. Thus, Huang[128] developed a mild and efficient Pd/C-catalysed monoalkylation of amino acids using alcohols as alkylating agents. Following this pioneering work, Hikawa[130] reported a methodology for mono-*N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol applying the homogeneous palladium-catalysed system in water as a reaction medium. Another work, described by Saito,[129] demonstrated the only example of the photocatalytic *N*-methylation of proline with methanol in the presence of a silver-loaded titanium dioxide (Ag/TiO_2). Our group disclosed the direct amination of the unprotected natural α-amino acids[123] and α-amino acid esters/amides[136] with alcohols (including long-chain fatty alcohols) in the presence of both Shvo's and Knölker's catalysts. Very recently, Ir(III)-NHC catalyst system was reported by Martín–Matute group that shows remarkable activity and broad scope in the *N*-alkylation of unprotected α-amino acids.[131]

3.2 Reductive amination

3.2.1 Mechanistic considerations. Reductive amination is one of the preferred catalytic pathways when obtaining bio-based amines from aldehydes or ketones inherently present in bio-based platform chemicals, such as sugars or important furane-derivatives, through the transformation of the C=O bond into a C–N one. It involves the reaction of an aldehyde or a ketone with an amine (including the industrially important ammonia). For a better understanding of the importance of this method and the challenges that still need to be tackled to transform this catalytic process into a cost-effective and elegant pathway towards bio-based amines, first one must have an insight into the mechanism. The general mechanism of this process is presented below in Fig. 5 showing the complexity and some challenges of this transformation. Detailed studies can be found in relevant reviews.[24,25,137] In the first step of the reductive amination, the carbonyl group is subjected to nucleophilic attack by the amine to form a hemiaminal intermediate, which dehydrates to afford the desired imine. In the second step, the resulting imine is reduced to the final amine product.

It is worth mentioning that reductive amination using ammonia would be an excellent method to form important primary amines, however, this transformation is typically highly challenging. This is not only due to the relatively sluggish imine formation step, but also due to the fact that the formed primary amines are generally better nucleophiles than ammonia itself, leading to the competing formation of secondary and tertiary amines, resulting in loss of selectivity. Mechanistically, with primary amine substrates, giving secondary amine products, the situation is similar to the case of ammonia. Differences occur when a secondary amine is used as substrate: instead of imine, an enamine is formed, which then is reduced to the desired tertiary amine. A further limitation may be that C=O reduction is more favoured than C=N reduction, leading to the competing hydrogenation of the substrate. Also, in the case of sluggish imine formation or imine reduction, the carbonyl compound itself can undergo aldol condensation reactions, diminishing product selectivity. Additionally, some reactive imine intermediates can also undergo condensation reactions, further compromising product selectivity. These side reactions can be avoided with the right selection of the catalytic system and optimization of reaction conditions to have the selective formation of the imine or enamine instead of the hydrogenation of the carbonyl substrate and hydrogenation of the imine (or enamine) at a high rate, preventing side reactions.[24,25] Thus, the key rate-limiting steps in reductive amination are: (a) imine formation, (b)

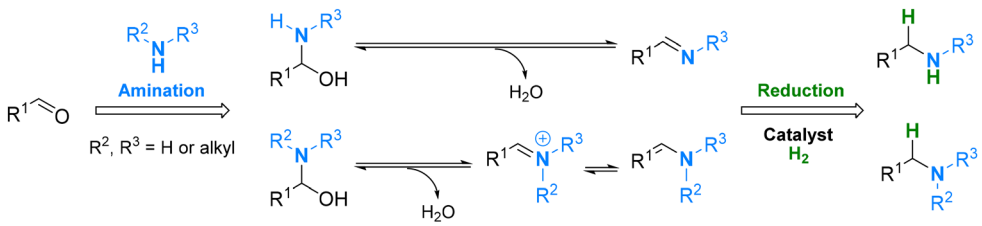

Fig. 5 General mechanism of reductive amination.

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imine reduction, which depends on the catalyst system utilized.

As described below, the most atom-economic and desired way to perform reductive amination is with molecular hydrogen (or hydrogen donor), which requires carefully designed catalyst systems for efficient hydrogen activation.

3.2.2 General considerations regarding reductive amination. Reductive aminations are key reactions in the chemical and pharmaceutical industries. Roughley *et al.* recently reported that a quarter of C–N bond-reactions for pharma synthesis are accomplished *via* reductive amination.[138] Furthermore, this method is the most utilized to prepare low carbon chain (C2–C5) amines, industrially relevant compounds in pharmaceutical, polymer and catalysis applications.[139] Reductive aminations are classically carried out using different metal hydrides[106] (*e.g.* sodium borohydride $NaBH_4$, sodium cyanoborohydride $NaBH_3CN$), silanes, which are usually used in stoichiometric quantities, resulting in significant by-product formation. In this context, molecular hydrogen has been proven as an ideal green replacement for commonly used reducing agents, allowing to minimize waste and by-product generation. It is worth noting here that the development of reductive amination approaches using molecular hydrogen is inseparable from the development of effective catalysts and methods for hydrogen activation.[24,25,42,140] Over the years, a series of heterogeneous and homogeneous catalysts have been designed for the synthesis of a wide range of amines from aldehydes or ketones through reductive amination.[25] To figure out what a good catalytic system should look like to achieve this goal, many studies have been conducted that have identified several aspects of a good and effective catalyst. Thus, in the case of homogeneous systems, organometallic catalysts must be highly selective with respect to the target product, tolerant to the functional groups of substrates, be stable under reaction conditions (avoid deactivation in the presence of ammonia, do not decompose at reaction temperature and pressure), promote proton exchange, form active forms of metal hydrides in the presence of H_2 and NH_3. The heterogeneous catalyst must also be selective, active, and stable, not suffer from metal leaching, be reusable for several cycles without deactivation, and be easily separated from the reaction mixture.[24,25,137,141] The most widely used homogeneous catalysts are based on noble metals such as rhodium, ruthenium, palladium, iridium; these precious metal-based catalysts are capable of facile formation of stable hydrides, and are able to stabilize metal (0) species in the catalytic cycle. However, the limited availability, high price, toxicity of these metals have prompted the investigation of earth-abundant metal-based catalysts. Recently, examples of cobalt, nickel, iron-based catalyst systems have emerged[24,25,142–144] that generally make use of strongly coordinating and electron-donating ligands, or operate through metal–ligand cooperation.[25,142]

Among the heterogeneous catalysts used for reductive amination reactions, RANEY® Ni, different supported ruthenium, cobalt, nickel catalysts, carbon-supported Ru, Rh, Pd, Pt are known to be effective for the formation of the target amine products.[24,25,142,144,145]

The case of using ammonia as a coupling partner to obtain primary amines deserves special mention. When developing a catalytic system for such a transformation, a number of difficulties must be taken into account. For the homogeneous catalyst system, the deactivation of the metal catalyst can take place as the ammonia coordinates to the metal, forming stable Warner-type complexes;[24,25] for the heterogeneous systems – irreversible adsorption of reagents on its surface or leaching of the active metal or support, as well as sintering. Fortunately, all these challenges can be solved by proper selection of the catalyst system, namely the catalyst itself and reaction conditions.[24,25,142,143]

3.2.3 Biomass-derived precursors for the synthesis of bio-based amines by reductive amination. The application of reductive amination for the synthesis of bio-based amines is more frequently encountered starting from the platform chemicals derived, in particular, from cellulose or hemicellulose (Table 3). Substrates such as glycolaldehyde, glyceraldehyde, furfural, or 5-hydroxymethyl furfural (5-HMF) are often upgraded through reductive amination.[24,42,146–150]

Carbohydrate derivatives. Glycolaldehyde is an important bio-derived substrate that can be sourced from cellulose or sugars through retro–aldol reactions or from pyrolysis oil.[148] It constitutes a C2 platform chemical and can lead to ethylenediamine, ethanolamine (monoethanolamine), diethanolamine, or piperazine through reductive amination pathways in the presence of NH_3, H_2, and a suitable catalyst. These products are industrially relevant: ethanolamine is used as an intermediate for pharmaceuticals, surfactants, or cosmetics.[148] Its industrial synthetic route typically involves chlorination or epoxidation of petrol-based ethylene utilizing ethylene oxide as an intermediate, which is a toxic, highly reactive compound. In this context, obtaining ethanolamine from bio-derived glycolaldehyde by reductive amination is a safer and more sustainable route. Different catalytic systems are known for this transformation.[42,106] For example, using a Ru/ZrO_2 catalyst Zhang and coworkers prepared amines from bio-based aldehydes or ketones in aqueous ammonia.[146] In these conditions (water) ethanolamine was synthesized with 93% yield when starting from glycolaldehyde and with 10% yield directly from cellulose in a two-step process.[146] Later, Sels and his team[148] underlined the importance of the choice of solvent, catalyst, and amine to glycolaldehyde ratio in the reductive amination of glycolaldehyde for producing alkanolamines. They developed various effective catalytic routes to several C2 amines (ethyleneamine, alkanolamines, ethylene diamines, higher alkanolamines) starting from glycolaldehyde using heterogeneous catalysts (Ni, Co, Pd, Ru – based), aqueous ammonia or corresponding amines and pressurized H_2 gas.

Other versatile important platform chemicals derived from cellulosic biomass or sugars through established dehydration pathways are furfural and 5-hydroxymethyl furfural (5-HMF).[89,107,109,149,151,152]

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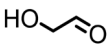
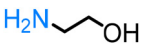
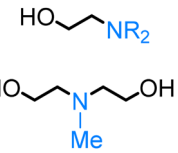
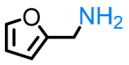
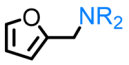
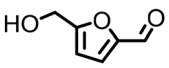
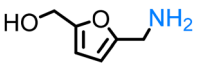
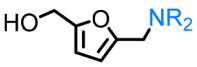
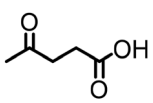
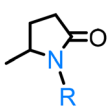
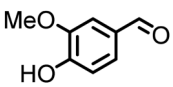
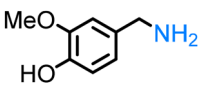
Table 3 Bio-based substrates as potential precursors for the synthesis of amines *via* reductive amination

Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
(Hemi) cellulose		Ru/ZrO_2, H_2 30 bar, aq ammonia, 75 °C, 12 hr		0.120 g (2 mmol)	2 mmol	R : H, 93%	146
		Ni-6458P (56 wt.%) or RANEY® Co-2725, 70 bar H_2, aq ammonia, 100 °C, 1 hr		0.500 g (8.3 mmol)	8.3 mmol	R : H, 35–45%	148
		Pd/C, 70 bar H_2, aq ammonia/amine, 100 °C, 1 hr		0.500 g (8.3 mmol)	8.3 mmol	R : H, Me, 28–91%	148
		$Ru/\gamma\text{-}Al_2O_3$, 30 bar H_2, 4 bar NH_3, MeOH, 80 °C, 2 hr		0.634 g (6.6 mmol)	6.6 mmol	R : H, 75%	153
		Ru/Nb_2O_5, 40 bar H_2, 1 bar NH_3, MeOH, 90 °C, 2 hr		0.048 g (0.5 mmol)	0.5 mmol	R : H, 99%	154
		$Au/SiO_2\text{-}SO_3H$, $Pt/SiO_2\text{-}SO_3H$, $Ir/SiO_2\text{-}SO_3H$, 0.1M sol of amine, 50 bar H_2, EtOAc, r.t., 8 hr		0.577 g (6 mmol)	5 mmol	R : H, 3–21%	161
		Ru1/NC-900-800NH_3, 20 bar H_2, 5 bar NH_3, MeOH, 100 °C, 10 hr		0.192 g (2 mmol)	2 mmol	R : H, 94%	160
		NiAl-10, MeOH, 20 bar H_2, 5 bar NH_3, 80 °C, 1.5 hr		1.16 g (12 mmol)	12 mmol	R : H, 99%	155
		Co-DABCO-TPA@C-800, 40 bar H_2, 5 to 7 bar NH_3, *t*-BuOH, 120 °C, 15 hr		0.063 g (0.5 mmol)	0.5 mmol	R : H, 89%	162
		Ru/Nb_2O_5, 1 bar NH_3, 40 bar H_2, MeOH, 90 °C, 4 hr		0.063 g (0.5 mmol)	0.5 mmol	R : H, 96%	154
		Ni_6AlO_x, 21 : 1 NH_3/HMF, 10 bar H_2, H_2O, 90 °C, 12 hr		3 g (23.8 mmol)	23.8 mmol	R : H, 81%	163
		1%Pd/C, 3 bar H_2, trifluorotoluene, 100 °C, 1–3 hr		0.126 g (1 mmol)	1 mmol	R : Alk, Ar 76–100%	164
		$Ru(DMP)_2Cl_2$, amine, 12 bar H_2, EtOH, 60 °C, 5–24 hr		0.063 g (0.5 mmol)	0.5 mmol	R : Alk, Ar 43–95%	165
		Pt-MoO_x/TiO_2, amine, 3 bar of H_2, solvent-free, 100 °C, 20 hr		0.116 g (1 mmol)	1 mmol	R : Alk, Ar 77–95%	166
		Pd/ZrO_2, amine, 5 bar of H_2, 90 °C, 12 hr		0.581 g (5 mmol)	5 mmol	R : Alk, Ar 80–94%	167
		Ru/NMC, amine, 15 bar H_2, ethanol, 120 °C, 4 hr		1.16 g (10 mmol)	10 mmol	R : Alk, Ar 80–99%	168
		(*R*)-[RuCl(*p*-cymene)(BINAP)]Cl, NH_4OAc, $Ti(Oi\text{-}Pr)_4$, TFE, 60 bar H_2, 90 °C, 22 hr		0.058 g (0.5 mmol)	0.5 mmol	R : H, 89%	169
Lignin		Rh/Al_2O_3, aq ammonia sol, 20 bar H_2, 80 °C		0.2 g (1.3 mmol)	1.3 mmol	91%	170
		Co-DABCO-TPA@C-800, 40 bar H_2, 5 to 7 bar NH_3, *t*-BuOH, 120 °C, 15 hr		0.076 g (0.5 mmol)	0.5 mmol	88% (SM: isovanillin)	162
		Ni_6AlO_x, 49 : 1 NH_3/aldehyde, 2 bar H_2, H_2O, 100 °C, 10 hr		0.152 g (1 mmol)	1 mmol	82%	163
		NiAl-10, THF, 30 bar H_2, 5 bar NH_3, 90 °C, 1 hr		0.152 g (1 mmol)	1 mmol	96%	155
		$Ni(BF_4)_2{\cdot}6H_2O$, triphos, 5–7 bar NH_3, 40 bar H_2, TFE, 100 °C, 24 hr		0.076 g (0.5 mmol)	0.5 mmol	90% (SM: isovanillin)	171

Selective reductive amination of furfural, with NH_3, leads to furfurylamine.[24,42,145,147] For example, with heterogeneous Ru/$\gamma\text{-}Al_2O_3$ under mild conditions, Dong *et al.* reported the production of primary amines from furfurylamine with 75% yield.[153] The key to high product selectivity was the choice of amphoteric alumina $\gamma\text{-}Al_2O_3$ support. The importance of the support was also shown by Hara and coworkers:[154] they observed that Nb_2O_5-supported ruthenium catalysts were the most efficient for the selective transformation of furfural to furfurylamine with 99% yield. Also, a nickel-containing catalyst was used for the switchable transformation of 5-HMF, presented by Wang.[155] The particularity of the catalyst is that by adjusting the particle size of the carbon-doped Ni nanoparticles grafted on hollow polymer nanospheres, the product of the reductive amination can be switched between the primary amine or the secondary imine, in both cases with excellent yield. Besides furfural, the catalyst could be used on other biomass-derived substrates such as 5-HMF or vanillin.

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The selective synthesis of furfurylamine from furfural has been investigated by several research groups, leading to the development of various heterogeneous catalysts based on ruthenium[156,157] as well as earth-abundant metals. For instance, single-crystal cobalt phosphide nanorods (Co_2P NRs),[158] working in aqueous ammonia and low H_2 pressure, or RANEY® cobalt.[159] The latter catalyst, under mild reaction conditions, gave the target product with good selectivity, which is explained by its efficiency at the hydrogenolysis step. Recently, Zhang reported a highly active N-doped carbon-supported ruthenium single-atom catalyst Ru_1/NC-900-800NH_3 for the selective production of primary amines. The catalyst exhibits good reuse stability and can be applied to other biomass-derived aldehydes (furfural, 5-HMF, glycolaldehyde).[160]

Equally well studied is the reaction of furfural with various primary or secondary amines leading to the formation of secondary or tertiary amines using heterogeneous catalytic systems,[24,25,145] such as sulfonic acid-functionalized silica-supported Au, Pt, and Ir catalyst systems shown by Martinez *et al.*[161]

5-HMF, one of the most important and versatile sugar-derived platform chemicals, has the potential to serve as a precursor for various amines. Interestingly, the selective reductive amination of the aldehyde functionality can be accomplished with ammonia in the presence of a suitable catalyst.[149] For example, with the catalytic system mentioned earlier for furfural, namely the Ru/Nb_2O_5 catalyst, Hara and coworkers showed the formation of 5-aminomethyl-2-furylmethanol with 96% yield.[154] MOF-derived cobalt nanoparticles Co-DABCO-TPA@C-800 prepared by Beller and his team have been successfully used for the amination of various aldehydes, including 5-HMF.[162] A nickel-based catalyst Ni_6AlO_x was developed by Pera-Titus and Shi with coworkers, delivering 5-aminomethyl-2-furylmethanol with excellent selectivity.[163]

When 5-HMF reacts with a primary or secondary amine, instead of ammonia, the corresponding *N*-substituted-5-(hydroxymethyl)-2-furfuryl amines are formed.[147,163–165] For example, Zhang and team described a homogeneous ruthenium complex, dichlorobis(2,9-dimethyl-1,10-phenanthroline)-ruthenium(II) ($Ru(DMP)_2Cl_2$), that gave the desired secondary or tertiary amines from 5-HMF in good yields (60–95%).[165] Corma and Iborra demonstrated a highly selective catalytic system, supported Pd nanoparticles (Pd/C), in the reaction of 5-HMF with aniline, which delivered *N*-phenyl-5-(hydroxymethyl)-2-furfuryl amine in quantitative yield.[164] A series of secondary and tertiary amines derived from 5-HMF were prepared by Pera-Titus and Shi, with substrates such as benzylamine, aniline, morpholine, 1-butylamine, and ethanolamine, using a Ni_6AlO_x catalyst.[163] Several other catalytic systems were presented for the transformation of 5-HMF into amines, both with noble (Pd, Ru) and earth-abundant metals (Ni, Co, Cu),[149,152] highlighting the significance of different methods for upgrading this biomass-derived precursor.

An interesting example of reductive amination of carbohydrate-derived chemicals can be found in the case of levulinic acid. In the first step, reductive amination of the carbonyl group takes place, followed by dehydrative cyclization of the amine and carboxylic groups, leading to the corresponding *N*-substituted 5-methyl-2-pyrrolidones. Shimizu *et al.* used a Pt-MoO_x/TiO_2 catalyst for the transformation of levulinic acid into a series of 5-methyl-2-pyrrolidones under mild, solvent-free conditions.[166] The reusable heterogenous catalytic system was successfully employed with a wide variety of amines leading to very good yields (>80%). Later, Zheng and Xiao *et al.*[167] emphasized that the catalyst plays an important role in the reaction to obtain the pyrrolidone rather than gamma-valerolactone, which is usually formed from levulinic acid by hydrogenation. Using ZrO_2-supported Pd nanoparticles, pyrrolidines could be produced from levulinic acid and various amines, and the high chemoselectivity of the catalyst was attributed to the strong Lewis acidity of the ZrO_2 support. Excellent yields (80% to 99.8%) could be achieved using a highly stable and recyclable N-doped mesoporous carbon (NMC)-supported Ru catalyst as well.[168] Recently, de Vries and coworkers synthesized chiral 5-methyl-2-pyrrolidinone from levulinic acid through asymmetric reductive amination employing a commercially available homogeneous ruthenium-bisphosphine catalyst. The (*R*)-[RuCl(*p*-cymene)(BINAP)]Cl catalyst using ammonium acetate as an amine source afforded the target product with 96% ee in 89% yield.[169]

Lignin derivatives. Reductive amination can also be employed on lignin-derived monomers. As such, vanillin (4-hydroxy-3-methoxybenzaldehyde) in an aqueous ammonia solution over a Rh/Al_2O_3 catalyst forms vanillylamine ((3-hydroxy-4-methoxyphenyl) methanamine) in good yield.[170] Other catalysts such as Ni_6AlO_x [163] or Co-DABCO-TPA@C-800[162] have been described for the conversion of vanillin to the corresponding primary amines.

Reductive amination of vanillin presents a few examples of homogeneous catalytic systems for the production of bio-derived amines. Such systems are based on Ru, Fe, Cu, Mn, Mo, Ir, Co complexes supported by different types of ligands.[24,25,142] Thus, with a nickel-based complex with triphos(bis(diphenylphosphinoethyl)phenylphosphine) ligand, vanillylamine was obtained with 90% yield in trifluoroethanol.[171]

Similar results were observed with a cobalt triphos catalyst (95% yield)[172] and $RuCl_2(PPh_3)_3$ complex (88% yield).[173]

3.3. Hydroamination of alkenes

3.3.1 Hydroamination of alkenes: general considerations. The hydroamination of alkenes is defined as the addition of an amine to a C=C bond forming a C–N bond, either in an intermolecular or intramolecular fashion (Fig. 6).[174–176] As the simplest amine, ammonia can also be used.[29] One of the key benefits from a green chemistry perspective is that the reaction proceeds with a complete atom economy, enabling the waste-free production of alkylamines from inexpensive and widely available starting materials.[42,177]

Hydroamination reactions are nearly energy-neutral processes ($\Delta G \sim 0$ kcal mol^{-1}).[178,179] Due to the thermoneutral nature of the reaction, the use of activated amines or alkenes is typically necessary.[180,181] Hydroamination of non-activated C=C bonds is more favorable in an intramolecular fashion, driven by ring-closing, and leading to nitrogen-containing heterocycles.[182]

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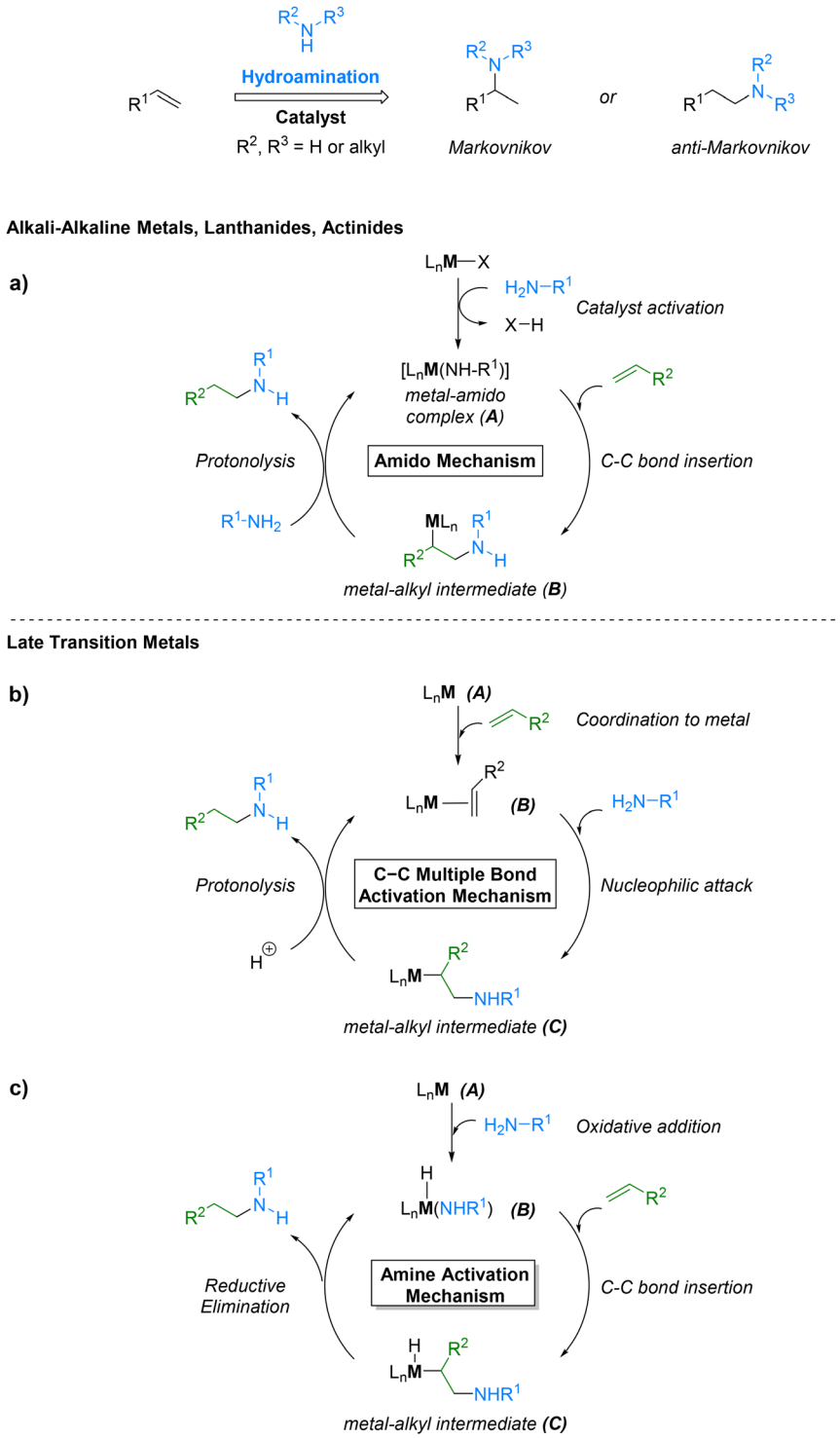

Fig. 6 General scheme of the hydroamination of alkenes and overview of mechanisms: (a) the amido-mechanism typical of alkali and alkaline metals, lanthanides and actinides; (b) the C–C multiple bond mechanism and (c) the amine activation mechanism that are typical of late transition metals. All mechanisms shown lead to the anti-Markovnikov product. The same pathways apply to the Markovnikov product, but are not depicted due to space constraints.

Hurdles that so far limited the development of efficient hydroamination reactions derive from the number of side reactions, such as isomerization and telomerization of alkenes, as well as oxidative amination.[183]

In the presence of metal-catalysed hydroamination reactions, the high affinity of σ donor amines with the metal centers employed as catalysts may inhibit their activity by preventing the coordination of the alkenes.[28,184] When ammonia

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is considered, high bond dissociation energy (415 kJ mol^{-1}), strong affinity with metal centres and high activation energy barrier to initiate the reaction are the major challenges that prevent it from being employed in alkene hydroamination reactions.[29]

The regioselective addition of the amine to the C=C bond also represents a key factor to consider (Fig. 6). Achieving anti-Markovnikov regioselectivity is highly preferred for obtaining industrially appealing linear primary amines.

Several catalytic systems have been explored over the last decades. Early studies predominantly employed alkali (Li, K, Cs), alkaline earth (Ca, Sr, Mg), actinides (U) and lanthanide (Nd, La, Lu, Sm, Y, Eu, Yb) metals as catalysts. It is generally accepted that reactions involving the use of these metals proceed *via* the so-called amido mechanism (Fig. 6a),[185] whereby the active metal–amido complex (A) is generated by protonolysis of the initial ligand by the amine substrate. This is followed by the insertion of the alkene into the metal–amido bond and the protonolysis of the M-alkyl species (B) by a new amine molecule to ultimately release the alkylamine and regenerate the catalytically active metal–amido species.

Later, group 4 metals (Ti and Zr) were also used as catalysts. Although these effectively facilitate amine addition to a wide range of alkenes, their high oxophilicity makes them sensitive to oxygen and moisture, restricting their use to controlled atmospheres and oxygen-free functional groups. These drawbacks prompted researchers to switch their focus to late-transition metals (Rh, Au, Cu, Pd, Ru, Pt, Ir).[28] Catalysts based on these metals display a C–C multiple bond activation mechanism (Fig. 6b).[186] This mechanism relies on the ability of cationic metal complexes with poor d-electrons to activate C–C multiple bonds by withdrawing electron density. This way, the nucleophilic amine attacks the metal-coordinated alkene (B) followed by protonolysis of M–C bond of the formed intermediate (C) giving rise to the hydroaminated product.

Importantly, late transition metals have been proposed to exhibit an amine activation mechanism as well (Fig. 6c). This involves the oxidative addition of an amine to generate an intermediate containing both a hydride and an amido group (B), followed by the insertion of a C=C bond into the M–N bond, resulting in intermediate (C), and final reductive elimination.[186,187]

For more detailed mechanistic and catalytic considerations, one may refer to the numerous excellent reviews.[28,174–176,183,184]

3.3.2 Biomass-derived precursors for the synthesis of bio-based amines by hydroamination. Hydroamination of alkenes derived from biomass offers a sustainable route for producing bio-based amines, leveraging renewable feedstocks. Various natural sources offer access to C=C bonds suitable for upgrading through hydroamination (Table 4).

Carbohydrate derivatives. The first hydroamination of ethylene, as the simplest alkene now accessible from bioethanol, dates back to 1954. In that year, Howk *et al.*[188] reported the sodium-catalysed addition of ammonia to ethylene under harsh conditions (175–200 °C, 800–1000 bar), producing nearly equimolar amounts of ethylamine, diethylamine, and triethylamine, with a total yield of 70%. Afterwards, Deeba and Ford[189,190] investigated the use of Zeolites, achieving a 13% yield of ethylamine. In 2005, Beller[191] reported a milder approach *via* base-catalysed hydroamination with diethylamine in the presence of $LiNEt_2$ at 80 °C and 40 bar, achieving up to 90% yield of the hydroaminated product.

Allyl alcohol is naturally present in garlic but it can also be obtained by hydrogenation of acrolein, which can in turn be derived from the dehydration of glycerol.[192,193] The anti-Markovnikov iron-catalysed hydroamination of allyl alcohols with aryl and aliphatic amines was demonstrated to access the γ-amino alcohols up to 99% yield by using Fe[194] as well as Mn catalysts. For example, Das *et al.*[195] investigated the use of Mn complexes bearing a soft sulfur donor side-arm in the *N*,*N* ligand backbone. Similarly, a PNP pincer complex was used by Duarte de Almeida *et al.*[196] for the hydroamination of allyl alcohol with *N*-aryl amines, leading to high product yield.

Tompos and colleagues[197] reacted diamines (Jeffamine polyether amines) with maleate and fumarate diesters, both with and without catalysts. Catalysts used included heterogeneous catalysts, such as $Ni(NO_3)_2$ on SiO_2, and organocatalysts like imidazole. However, the presence of catalysts resulted in only a modest increase in conversion rates, with yields improving by just around 10%.

The hydroamination of dimethyl maleate with aniline has been demonstrated using $NiBr_2$ and AgOTf, at 100 °C for 16 h, producing the corresponding *N*-aryl dimethylmaleate in 42% isolated yield.[198] Kunjanpillai and co-workers recently expanded the catalyst scope to $Ln(OTf)_3$, with the product isolated in 33% yield, at 100 °C for 24 h.[199]

As regards to amino alkenes, the lanthanocene-catalysed intramolecular hydroamination of 5-amino-1-pentene, which can be obtained from the dehydration of bio-based 5-amino-1-pentanol,[200] can form 2-methylpyrrolidine, as demonstrated by the Marks group.[201,202] Later, Ye and Zhu[203] investigated the intermolecular hydroamination of *N*-tosylated 5-amino-1-pentene by employing a cobalt catalyst, to produce *N*-tosylated 2-methylpyrrolidine derivatives. Recently, Hennecke and co-workers[204] reported the hydroamination of *N*-nosyl 5-amino-1-pentene. Hultzsch *et al.*[205] synthesized chiral rare-earth-metal (yttrium and lanthanide) complexes containing biphenolate and binaphtholate amido complexes, which were utilized for the hydroamination/cyclization of 5-amino-1-pentene. Complete conversion was achieved at 100 °C and a reaction time of 16 h, with a moderate enantiomeric excess (ee) of 52% for the *R*-product. Marks[206] obtained a medium ee 40%, *R*-product, employing lanthanide-based bis(oxazolinato) complexes, under ambient conditions. A significant improvement was achieved by Kim and Livinghouse[207] who utilized yttrium complexes of axially chiral bis(thiolate) ligands, achieving 81% ee. Sadow and co-workers[208] reported on the use of zwitterionic cyclopentadienyl-bis(2-oxazolinyl)borate diamidozirconium complexes as pre-catalyst for the hydroamination/cyclization of 5-amino-1-pentene at room temperature with a 62% yield.

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Table 4 Bio-based substrates as potential precursors for the synthesis of amines *via* hydroamination of alkenes

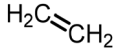
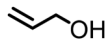
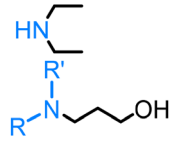
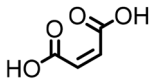
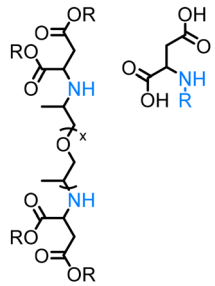
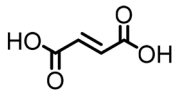
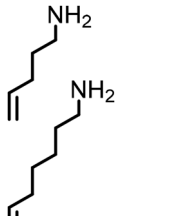
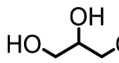
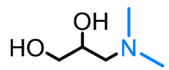
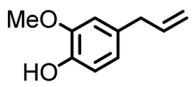
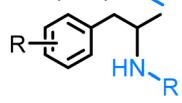
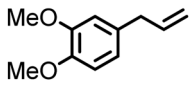
Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
(Hemi) cellulose		Na metal, 175–200 °C *n*-heptane, ammonia		800–1000 bar	2.94 moles	70%	188
		H-clinoptilolite, 370 °C, ammonia		11 bar	Not given	13%	189
		Lithium diethylamide, TMEDA, 80 °C, toluene, 18 hr		40 bar	0.03 mol amine	93%	191
		$[Fe(Cy_2PC_2H_4)_2NH)COBr_2]$, $NaHBEt_3$, K_3PO_4, cyclohexane, 80 °C, N_2, 12–24 hr		0.044–0.087 g (0.75–1.5 mmol)	0.5 mmol	53–99%	194
		$[Mn(Et_2PC_2H_4)_2NH)(CO)_2Br]$, $NaHBEt_3$, K_2CO_3, cyclohexane, 60 °C, Ar, 24 hr		0.058 g (1 mmol)	0.5 mmol	13–96%	196
		$[Mn(Ph\text{-}SMe)\text{-}Py)(CH_2)_2NH)(CO)_3Br]$, K_2CO_3, toluene, 100 °C, Ar, 24 hr		1.196 g (21.5 mmol)	5.37 mmol	74%	195
		$Ni(NO_3)_2$ on SiO_2, neat, RT, 2–24 hr		5.2 g (30 mmol)	15 mmol	76–84%	197
		$NiBr_2$, AgOTf, toluene, 100 °C, 16 hr		0.43–0.86 g (3–6 mmol)	2 mmol	42%	198
		$Ln(OTf)_3$, toluene, 100 °C, 24 hr		0.22–0.43 g (1.5–3 mmol)	1 mmol	33%	199
		$Cp_2'LaCH(TMS)$, pentane, RT, Ar, 24 hr		1.69 g (20 mmol)	20 mmol	86%	202
		$Y[H_2(Dip_2BINO)][N(SiHMe_2)_2](THF)_2$, benzene-$d_6$, 100 °C, Ar, 16 hr		0.032 g (0.38 mmol)	0.38 mmol	~99%	205
		$[(4R,5S)\text{-}Ph_2Box]La[N(TMS)_2]_2$, benzene-$d_6$, 23 °C, Ar		0.012 g (0.14 mmol)	0.14 mmol	~98%	206
		$Y[Bis(thiolate)][N(TMS)_2]$, thiophene, benzene-$d_6$, 60 °C, Ar, 8 hr		0.027 g (0.32 mmol)	0.32 mmol	81%	207
		$\{PhB(\eta^5\text{-}C_5H_4)(Ox^{Me2})_2\}Zr(NMe_2)_2$, benzene-$d_6$, 23 °C, Ar, 33 hr		0.009 g (0.1 mmol)	0.1 mmol	~62%	208
		(*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicyliden)-1,2-cyclohexandiaminocobalt(II) tosylate, TMDSO, NBu_4OTf, O_2, neat, RT, 6 hr		0.026 g (0.3 mmol)	0.3 mmol	78%	203
		$Y[H_2XN_2](CH_2SiMe_3)_3(THF)_2$, benzene-$d_6$, 60 °C, Ar, 45 min		Not given	Not given	~99%	209
		$Cs_{2.5}H_{0.5}PMo_{12}O_{40}$ on SiO_2, 290 °C, water, N_2, 3 hr		Not given	Not given	5%	210
Lignin		[Ir[(*S*)-DTBM-SEGPHOS](ethylene)(Cl)], NaBArF, 1,4-dioxane, 60 °C, N_2, 18–19 hr $Ru(PEt_3)_3NTf_2$, 1,2-dichlorobenzene, 80 °C, 48 hr		0.013–0.036 g (0.1–0.2 mmol)	0.1–0.2 mmol	52–95%	211 and 212
							

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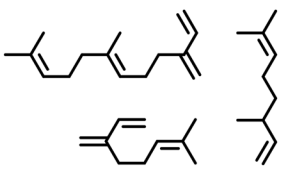
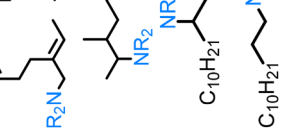
Table 4 (*Contd.*)

Type of biomass	Platform chemical (PC)	Reaction conditions (selected examples)	Amine product	Amount of PC required	Scale	Yield	Ref.
Terpenes		$Pd(tfa)_2$, DPEphos, DMF : heptane (40 : 60), 110 °C, Ar, 3 hr		Flow	Flow 0.1667 mol L^{-1}	80%	213
		$Pd(tfa)_2$, DPEphos, DMF, 100 °C, Ar, 5 hr		0.87 g (4 mmol)	4 mmol	94–99%	214
		$Ru(PEt_3)_3NTf_2$, 1,2-dichlorobenzene, 100 °C, 48 hr		0.022 g (0.2 mmol)	0.2 mmol	57%	211
Fatty alcohol & fatty acids		$Cu(OAc)_2$, (±)-DTBM-SEGPHOS, diethoxymethylsilane, 40 °C, Ar, 36 hr		0.381 g (1.2 mmol)	1 mmol	95%	215
		$Ru(PEt_3)_3NTf_2$, 1,2-dichlorobenzene, 80 °C, 48 hr		0.022 g (0.2 mmol)	0.2 mmol	63%	211
		[Ir[(*S*)-DTBM-SEGPHOS](ethylene)(Cl)], NaBArF, 1,4-dioxane, 60 °C, N_2, 18–19 hr		0.011 g (0.1 mmol)	0.1 mmol	81%	212

In a similar manner, 1-amino-5-hexene, a compound which can be obtained through the dehydration of 6-amino-1-hexenol, the corresponding 6-membered *N*-heterocycle can be obtained through different rare earth, yttrium or aluminum catalysed processes.[209]

While most alkenes used in hydroamination are derived from bio-based alcohols, a straightforward alternative would be to use the said alcohols directly. In one case, (dimethylamino)acetone was obtained from glycerol using a $Cs_{2.5}H_{0.5}PMo_{12}O_{40}$ supported on a mesoporous silica.[210]

Lignin derivatives. A few examples of lignin-derived compounds were successfully employed as renewable platform chemicals for the synthesis of amines *via* hydroamination. Hartwig and co-workers[211] studied the hydroamination of various unactivated terminal alkenes with ammonia surrogates (2-amino-5-methylpyridine) in the presence of $Ru(PEt_3)_3NTf_2$. In this regard, they evaluated the hydroamination of 4-allyl-1,2-dimethoxybenzene, which can be obtained from lignin-derived eugenol, with 2-amino-5-methylpyridine at 80 °C for 48 h, isolating the Markovnikov product in 52% yield. The pyridyl moiety can be removed in the presence of PtO_2, H_2 and $NaBH_4$, to afford the corresponding primary amine product. In a similar study, the same group also reported on the use of a chiral (*S*)-Ir catalyst for the hydroamination of estragole (1-allyl-*p*-methoxybenzene), chavicol (*p*-allylphenol) and eugenol.[212] The corresponding aminated products were isolated in excellent enantioselectivity and 86%, 92% and 95% yield, respectively.

Terpene derivatives. As naturally available unsaturated compounds, terpenes are a valuable source to obtain renewable amines *via* hydroamination. In this frame, Vorholt and co-workers[213] investigated the hydroamination of β-myrcene with morpholine, in the presence of a $Pd(tfa)_2$/Bis[(2-diphenylphosphino)phenyl]ether catalyst system. They have also expanded this to the hydroamination β-farnesene with dimethyl and diethyl amine, piperidine, morpholine and diethanolamine, using the same catalyst system as reported for β-myrcene.[214] The corresponding amines were isolated in moderate (48% in the case of diethanolamine) to excellent (94–99% for the other amines) yields at 100 °C for 5 h. Hartwig[212] studied the hydroamination of (+)-β-Citronellene, which can be obtained from citronellol, a monoterpenoid, using $Ru(PEt_3)_3NTf_2$ at 80 °C for 48 h. The hydroamination was performed in the presence of an ammonia surrogate (2-amino-5-methylpyridine), which can be removed in the presence of PtO_2, H_2 and $NaBH_4$, in order to produce the corresponding primary amine product in 57% isolated yield.

Fatty acids derivatives. The internal double of fatty acids/esters can also undergo hydroamination, resulting in renewable compounds which are of interest in the polymer industry. In this regard, the hydroamination of 1-dodecene, which can be obtained *via* the dehydration of 1-dodecanol, itself derived from bio-based lauric acid, has been investigated by Buchwald and co-workers.[215] In their work, they utilized copper phosphine catalysts, which were able to regioselectively catalyse the hydroamination of terminal alkenes to afford the anti-

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Markovnikov product. In the case of 1-dodecene with *O*-benzoylhydroxylamine, the corresponding aminated product was isolated in 94% yield, at 40 °C and 36 h reaction time. In contrast, the Markovnikov product derived from the hydroamination of 1-dodecene with 2-amino-5-methylpyridine, used as ammonia surrogate, was obtained by Ma *et al.*[211] in 63% yield. $Ru(PEt_3)_3NTf_2$ was utilized as catalyst, at 80 °C for 48 h. This was later expanded to the use of a chiral (*S*)-Ir catalyst for the hydroamination of the same substrates, where the product could be isolated in 81% and an er of 95 : 5 (*S*-product).[212]

4. Evaluation of the green credentials for the synthesis of amines: a comparative analysis

Having established the foundation of various catalytic amination approaches as applied to renewables, we now turn the focus on a comparative analysis between traditional petrochemical routes and bio-based synthesis methods for selected case studies. By employing the CHEM21 green metrics toolkit, we assess the environmental and operational sustainability of these pathways.

However, it is important to acknowledge the inherent differences between mature, well-established petrochemical processes and emerging bio-based technologies, whereby the developments regarding biorefineries and innovative solutions to access renewable platform chemicals are naturally lagging behind. Biorefinery approaches, especially those for processing complex non-edible lignocellulosic biomass are at the discovery or pilot stage, nonetheless a rapid progress is expected in the development of biorefineries towards higher TRL levels and commercial feasibility.

This presents a unique challenge when comparing the fossil-based *versus* bio-based approaches during our analysis. Therefore, our comparative analysis (sections 4.2–4.5) focuses on comparing the value chains even at laboratory stage development, but excludes raw material sourcing. A specific discussion on bio-based platform chemical sourcing is provided in section 4.1 below.

This means that a cradle-to-grave analysis of the entire process goes beyond the scope of this tutorial review.

4.1 Feedstock sourcing

Herein we provide a discussion on the starting reagents employed for the comparative analysis outlined afterwards. Except for cardanol (Scheme 3), all of the compounds selected as starting reagents for the bio-based synthetic routes are derived from lignocellulosic biomass. Specifically, dihydroconiferyl alcohol (Scheme 1) is derived from lignin, while 5-(chloromethyl)furfural (Scheme 2) and 5-hydroxymethyl furfural (Scheme 4) are derived from cellulose.

4.1.1 Dihydroconiferyl alcohol. Several seminal studies demonstrated the feasibility of obtaining dihydroconiferyl alcohol in one step from lignocellulose by applying reductive catalytic fractionation (RCF). While demonstrating the catalyst influence on the selectivity of birch wood RCF, the Sels group[216] discovered that Pd/C promotes the formation of phenolic alcohols, obtaining 9.7 wt% of dihydroconiferyl alcohol. One year later, the same group[217] investigated the influence of H_3PO_4 on the RCF of poplar lignin, demonstrating an increased yield toward dihydroconiferyl alcohol to 14 wt%. Shortly after, Barta and co-workers[9] managed to obtain dihydroconiferyl alcohol from pine lignocellulose in a remarkable selectivity (>90%) with a non-noble-metal catalyst (Cu20-PMO) under relatively mild conditions (180 °C). Hereby dihydroconiferyl alcohol was proposed as a viable lignin-derived platform chemical, which was converted to a range of products, including amines. Later, Luterbacher's group reported access to dihydroconiferyl alcohol *via* propionaldehyde-assisted fractionation, followed by Ni-catalysed hydrogenolysis.[218]

These reports reveal the feasibility of obtaining dihydroconiferyl alcohol from lignocellulose, positioning it as the ideal starting material for the pathways showcased in Scheme 1.

Although the production of fossil-based benzene may be assumed as more cost-effective, several LCA studies related to RCF exist in the literature.

Researchers have made remarkable strides, advancing RCF biorefining, by optimizing reaction conditions, screening catalysts, and enhancing experimental setups. However, recent techno-economic analysis (TEA) and life cycle assessment (LCA) have flagged the necessity of further developments to make RCF more economically viable.[219–221]

Tschulkow *et al.*[222] recently reported that woody biomass conversion into bleached pulp, phenolic monomers and oligomers currently generates higher greenhouse gas (GHG) emissions compared to alternative market options (unbleached sulfate pulp, phenol, and bisphenol A), largely due to by-products and gaseous waste streams. The authors provided alternatives that could reduce the emissions by up to 50%, such as incinerating gaseous waste streams for energy recovery. An additional challenge associated with the RCF process is the cost and recovery of pure solvents. Arts *et al.*[220] demonstrated that using solvent mixtures derived from RCF effluent improved lignin extraction while significantly reducing costs and environmental impact in terms of lignin oil minimum selling price (MSP-RLO) and global warming potential (GWP-RLO), making possible comparison with fossil-based routes. Beckham and Román-Leshkov groups[221] further explored the role of RCF recycled oil as a solvent for the RCF process, demonstrating that a concentration of lignin oil in the solvent up to 100 wt% is feasible while achieving similar performances of a methanol–water mixture.

An additional recommendation is to develop hydrogen-free RCF processes, as lowering reactors' operating pressures could reduce the RCF oil selling price by 32%. In this frame, encouraging results were disclosed by Kenny *et al.*[223] when using Pd/C and Pt/C on poplar lignin, as high monomer yields were retained while using these catalysts in the absence of H_2. Debecker[224] and coworkers investigated the role of different hydrogen donors for straw RCF. Notably, to prevent (hemi)cell-

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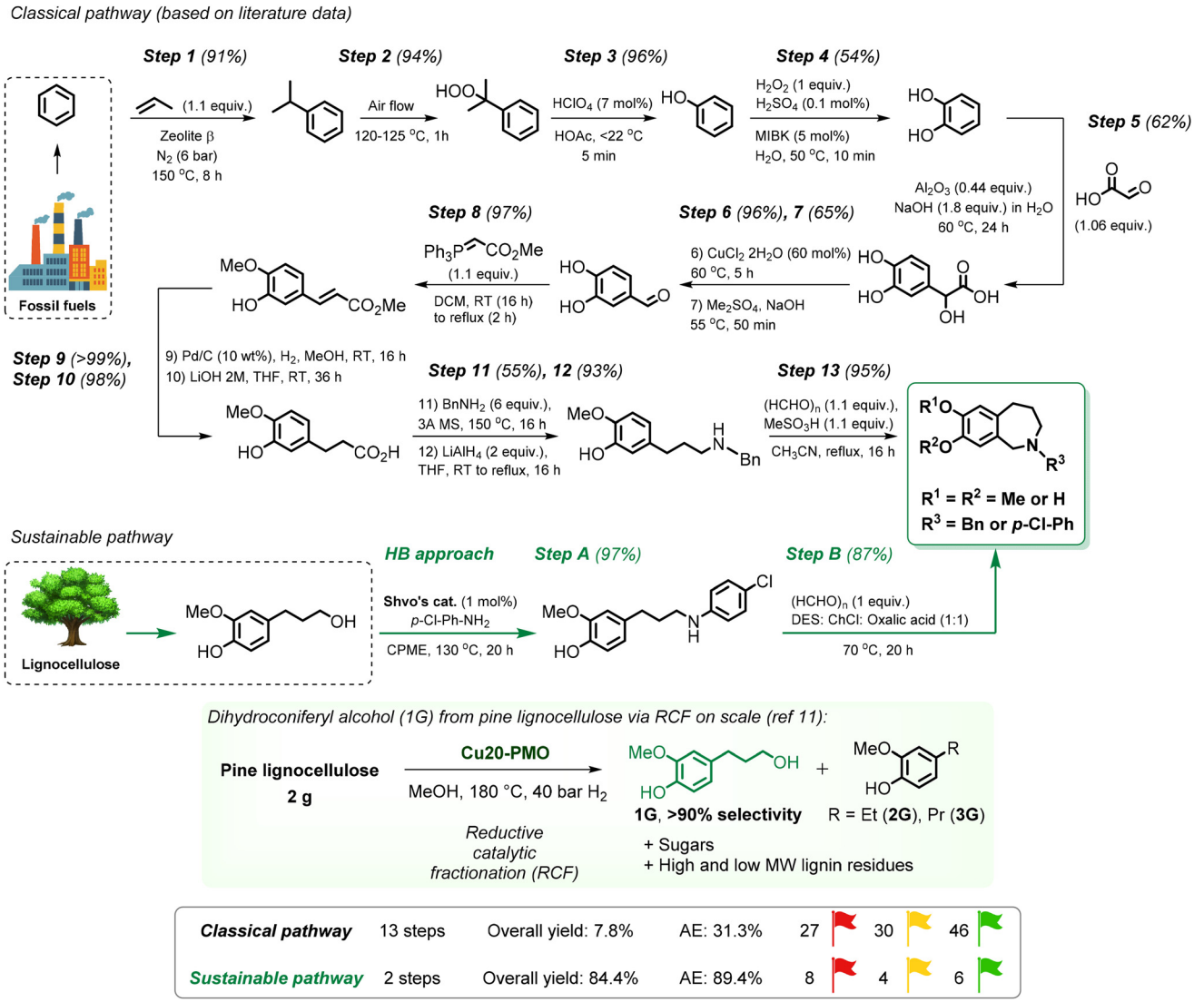

Scheme 1 Synthesis of *N*-substituted tetrahydro-2-benzazepines *via* a classical route (Steps 1–13) starting from benzene *vs.* a sustainable route (Steps A–B) starting from lignin-derived dihydroconiferyl alcohol.

ulose decomposition due to the high temperatures (250 °C), the use of H_3PO_4 boosted the generation of monophenolic compounds, enabling monomer yields to reach approximately 18 wt% in hydrogen-free conditions.

4.1.2 5-(Chloromethyl)furfural (CMF). For the comparative analysis regarding the synthesis of ranitidine, 5-(chloromethyl) furfural (CMF) is selected as the starting reagent for the alternative pathway, while furfural is chosen for the classical pathway. Both the reagents are renewable as they are derived from cellulose.

The synthesis of furfural from cellulose is a well-established process involving the H_2SO_4-promoted hydrolysis of pentosan sugars to monosaccharides (mainly xylose), followed by dehydration to furfural.[225,226] The produced furfural is recovered through steam distillation and fractionation. This process was first developed by Quaker Oats,[227] which started commercialising furfural in 1921, later followed by other companies that adopted similar methods based on the same process.[228] Side reactions occurring during the synthesis, *e.g.* formation of humins, are responsible for the typically low yields (~50%), which is acceptable for an industrial operation. Much research is currently devoted to optimizing furfural synthesis mainly focusing on the use of solid catalysts and biphasic systems.[229]

The Mascal group[230,231] has pioneered the synthesis of CMF from cellulose, which was found to be synthesized from corn stover with 72% yield in a biphasic reactor, under mild conditions, using aqueous HCl as the sole reagent. The main drawback in this case is related to the use of hazardous 1,2-dichloroethane solvent, which is used to create a phase separation that is not compromised by aqueous acid. Breeden *et al.*[232] investigated CMF synthesis *via* microwave heating using cyclopentyl methyl ether (CPME) and cyclohexane. Recently, Bueno Moron *et al.* integrated CMF production with selective lignocellulose saccharification (DAWN technology,

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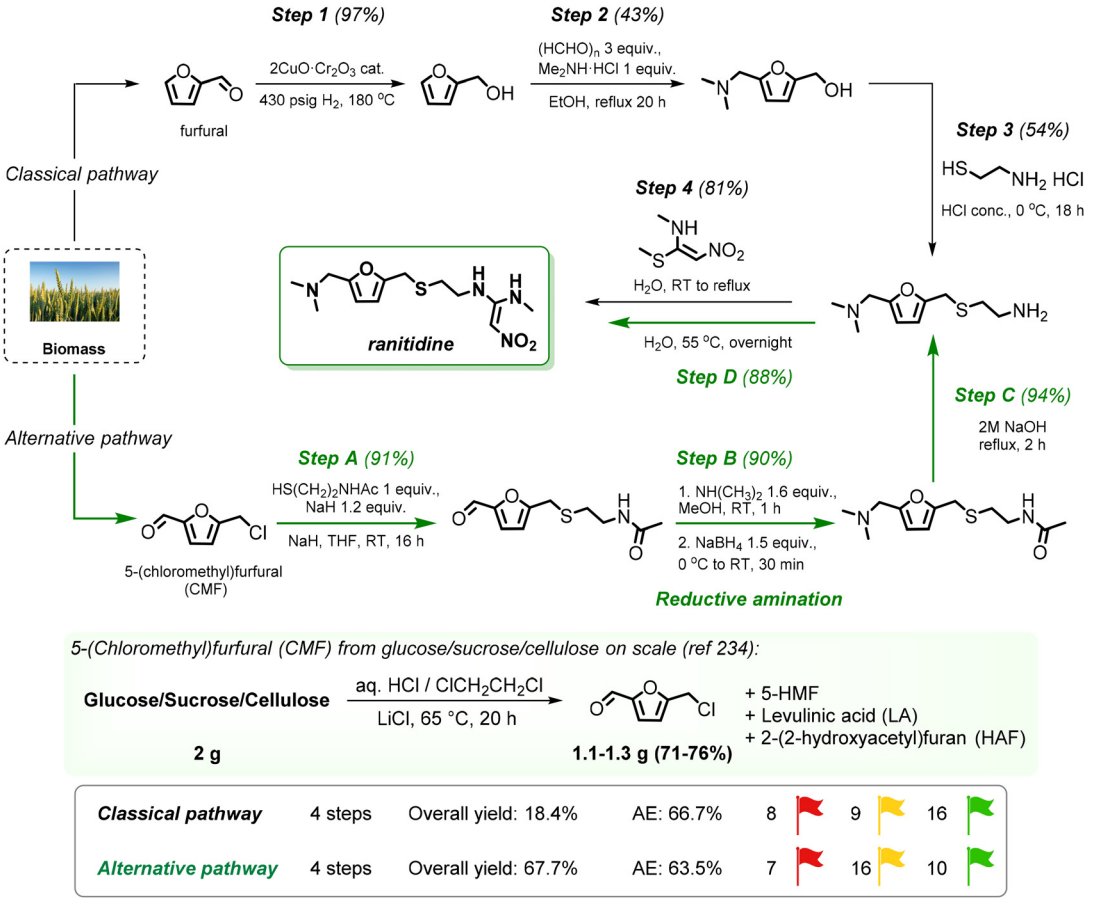

Scheme 2 Synthesis of ranitidine by the classical pathway (Steps 1–4) *vs.* the alternative pathway (Steps A–D).

Avantium), optimizing a biphasic system to enhance yields (>90%) and scalability.[233]

Nowadays, bio-CMF is commercialized by Origin Materials,[234–236] making it a suitable candidate for the sustainable synthesis of ranitidine.

4.1.3 Cardanol. Cardanol, selected as the starting reagent for the bio-based synthesis of norfenefrine (Scheme 3), is derived from cashew nut shell liquid (CNSL). This commercially available mixture of phenolics is heated to induce decarboxylation of anacardic acid to yield 60–65% cardanol-rich oil. Cardanol is an inedible by-product from the food industry which was found to be a valuable starting reagent for the production of norfenefrine by the Cole-Hamilton group.[237] In the same study, the authors were able to isolate cardanol from CNSL *via* a mild two-step process. In the first step, 11 grams of anacardic acid (55% yield) were isolated from CNSL. Afterwards, cardanol was obtained in high yield (98.6%) by simply heating ancaradic acid at 200 °C. However, there is currently no LCA data available to compare the sourcing of cardanol and benzene.

4.1.4 5-(Hydroxymethyl)furfural (HMF). The synthesis of hexane-1,6-diamine (1,6-HMDA, Scheme 4) is discussed by considering the commercial process, starting from petrol-based butadiene, and two sustainable pathways, both starting from fructose syrup derived from maize and potato-based starch, with HMF serving as an intermediate building block.

5-HMF is an ideal building block for producing bio-HMDA given its facile access from carbohydrates *via* catalytic dehydration of pentoses. Having multiple functional groups, such as carbonyl and hydroxyl, within its structure, this compound provides opportunities for further functionalization in an atom- and step-efficient manner.[93,238] Nevertheless, the challenge persists in achieving the selective conversion of 5-HMF into the desired product, given its heightened reactivity. For example, Dros *et al.*[239] highlighted that based on current technologies, the petrochemical-based synthesis of hexamethylenediamine (HMDA) is more economically and environmentally favourable than bio-based alternatives due to lower manufacturing costs (1.84 € per kg *vs.* 2.13–2.55 € per kg) and high impact on eutrophication derived from the use of fertilizer-intensive feedstocks. The main issues are related to the feedstock used for fructose production and the high energy demand needed to dry the high-fructose syrup (HFS) used in the production of HMF. Therefore, it could seem impractical to compare the HMF-based route with a conventional one based on a bulk petrol-based chemical such as butadiene. However, the authors highlighted promising alternatives which should focus on optimizing synthetic strategies to

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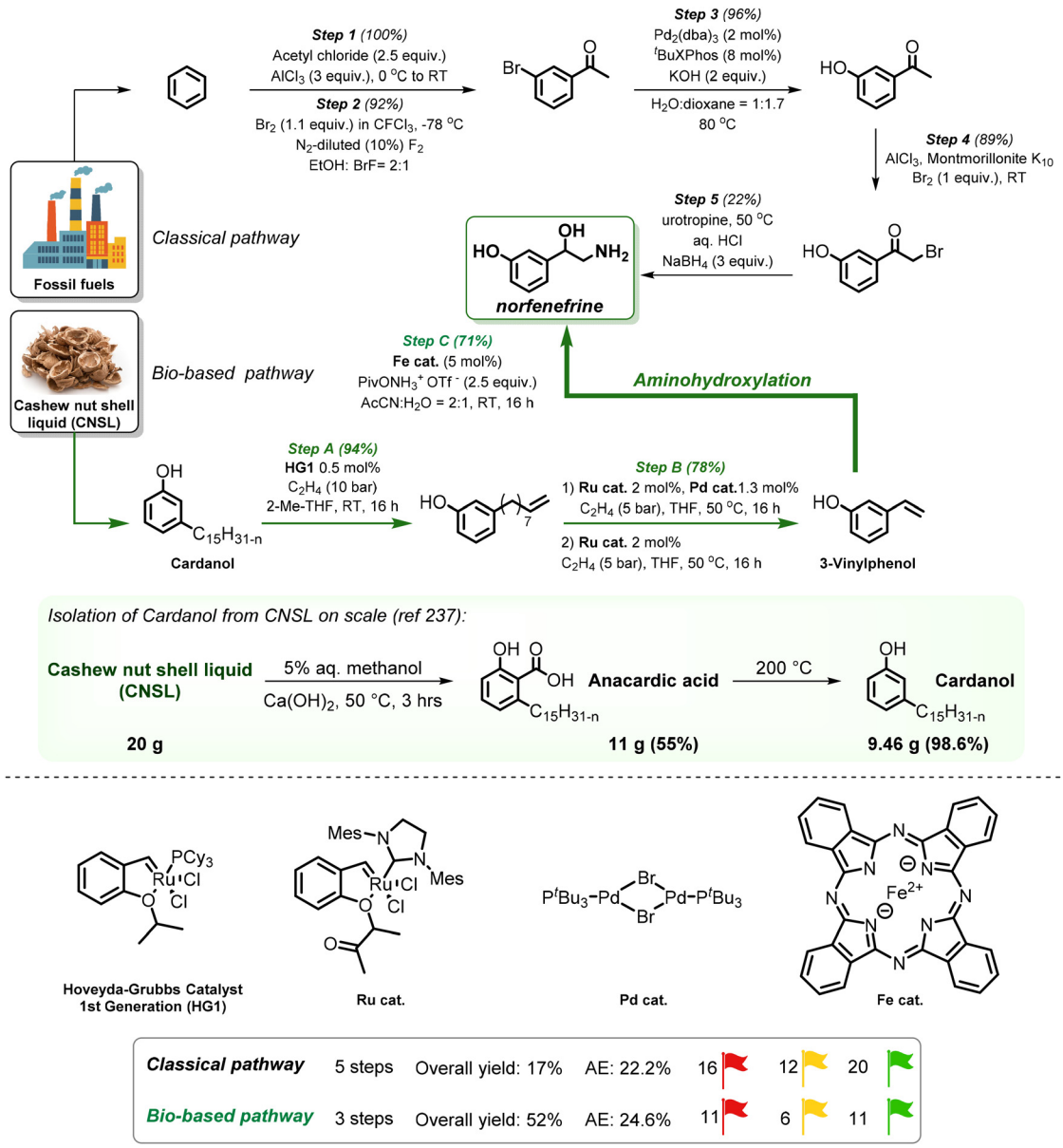

Scheme 3 Synthesis of norfenefrine by the classical pathway (Steps 1–5) *vs.* the bio-based pathway (Steps A–C).

produce fructose (and HMF) directly from agricultural lignocellulose and on using aqueous or biphasic systems to reduce the need for costly and environmentally impacting drying procedures and extensive use of organic solvents. Several studies have already shown encouraging results in this context.[240–243]

4.2 Evaluation of the green credentials for the synthesis of *N*-substituted tetrahydro-2-benzazepines

In order to demonstrate the efficiency and potential of the 'hydrogen borrowing' methodology, herein we perform a comparative analysis in terms of the greenness of a classical, literature-based, and sustainable protocol based on the 'hydrogen borrowing' approach for the synthesis of *N*-substituted tetrahydro-2-benzazepines.

We selected two examples, namely 2-benzyl-8-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-7-ol and 2-(4-chlorophenyl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-8-ol since for these compounds well-described and detailed experimental petroleum-based[244–249] and bio-based[11] synthetic procedures are available in the literature. These literature pathways are at the discovery level – first pass CHEM21 green metrics toolkit.

The values of quantitative (calculated for each step and overall route) and qualitative metrics for both the classical and sustainable approaches are summarised in Scheme 1 and Tables S2 and S3 (see ESI for more details†). On the whole, the results of the analysis of the quantitative and qualitative metrics demonstrate a clear advantage of the sustainable

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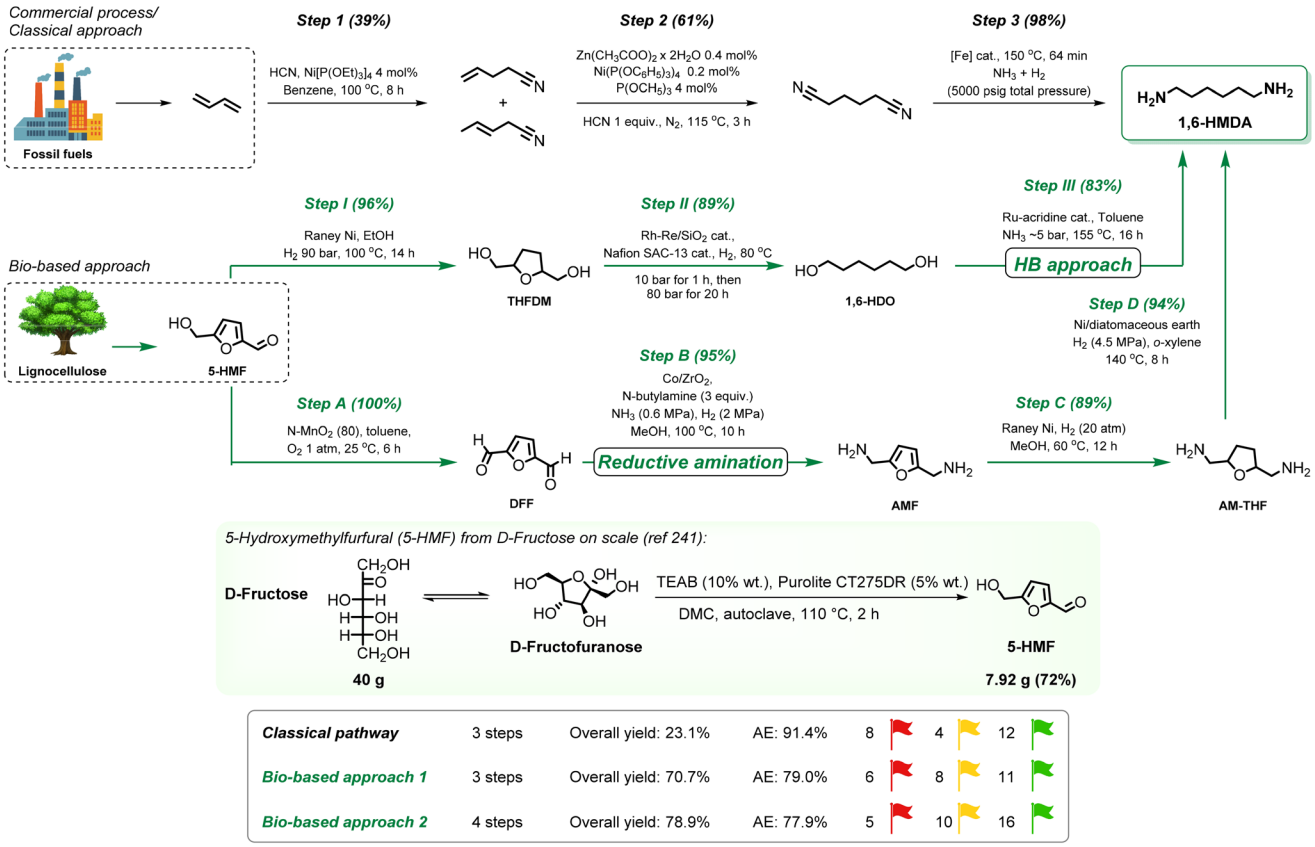

Scheme 4 Synthesis of HMDA: comparison of the commercial route with sustainable approaches based on reductive amination and 'hydrogen borrowing' atom-economic transformations.

approach over the classical one; below the obtained results and each evaluated parameter are discussed in detail.

When comparing mass-based metrics of the two approaches toward *N*-substituted tetrahydro-2-benzazepines (Scheme 1 and Table S2†), it is obvious that the step economy of the sustainable one is higher: only 2 steps are required to obtain *N*-substituted 7-membered heterocycle starting from lignin-derived dihydroconiferyl alcohol, compared to 13 steps in the classical approach from benzene. As such, the yield of the former is almost 11 times higher (84.4% *vs.* 7.8%)! The same trend is observed for AE and RME: for the green path, both parameters are increased to 89% and 67%, correspondingly, compared to 31% and 5% for the classical route. Fewer reaction steps significantly reduce waste production: PMI tot reduced by 72% (3866 g g^{-1} *vs.* 1082.3 g g^{-1}). The latter is promising, given the fact that the sustainable route entirely consists of steps for which only data on the discovery level are available. Moreover, it can be expected that further optimization of the reaction conditions, the solvent used in each step as well as the solvent recycling, and the work-up method when moving toward the pilot scale will make the sustainable route even greener compared to the classical one. It is worth mentioning that cumulative PMI values contain the PMIs WU that were not optimized at the discovery level, as such comparison and interpretation of cumulative overall PMIs should be performed with caution.

Looking at the qualitative parameters (Scheme 1 and Table S3†), it can be seen that the sustainable pathway uses a biomass-derived substrate, dihydroconiferyl alcohol, which scores higher in the 'health and safety' category than the reactants benzene and cumene. Both petrochemical substrates, benzene, and cumene, receive red flags (benzene: H340, H350, H372, H410; cumene: H411), while lignin-derived dihydroconiferyl alcohol receives a yellow label (H351). In the analysis of other chemicals used in the green route, only three red flags were received for the 'health and safety', namely *p*-chloroaniline, paraformaldehyde, and pentane, while the classical method requires the use of catechol, $CuCl_2$ $2H_2O$, $LiAlH_4$, benzylamine, *etc.*, resulting in many additional red flags.

Regarding the reaction solvent used, yellow and green flags are obtained (CPME and DES in Steps A and B) in the green path, in contrast to the literature-based approach which is scored with a red flag (DCM in Step 8) and 3 yellow flags (THF, CH_3CN in Steps 10, 12, 13).

For critical elements, a red flag is obtained due to the use of a Ru-based Shvo's catalyst in Step A of the alternative route. In the classical pathway, 10 yellow labels are obtained using Al, S, Cu, Li, Pd, and P-containing reagents.

Concerning the chemical requirements, it can be noted that in the alternative route, the amination of the dihydroconiferyl alcohol is a catalytic transformation that utilizes a small

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loading of ruthenium-based Shvo's catalyst (green flag), while the acid-catalysed Pictet–Spengler cyclization takes place in presence of the stoichiometric amount of deep eutectic solvent (yellow flag). In fact, this class of promising solvents displays the behaviour of a non-innocent, low vapour-pressure reaction media, acting both as a catalyst and a solvent, resulting in milder reaction conditions and improved reaction selectivity. This recyclable reaction media has proven itself as a benign replacement for conventional organic solvents and mineral corrosive acids. In a classical route, most of the reaction steps (9 out of 13) require excess or stoichiometric amounts of reagents (red and yellow flags, respectively).

Considering energy requirements, in the new path, Step A obtains a red flag due to the reflux conditions (130 °C) using CPME as a solvent (boiling point of CPME is 106 °C); Step B receives a green flag using DES as a reagent and a solvent at 70 °C. The classical route gets six red flags for energy requirement since all of these steps require harsh reaction conditions (under reflux). Also, given that the number of steps for the alternative route is significantly less compared to the literature-based approach, the overall energy consumption for the former one is more beneficial. Considering the work-up, the bio-based approach involves the use of column chromatography in both steps, resulting in two red flags. However, as it was mentioned above, in this case, work-up methods were not optimized at the discovery level, which opens up the possibility of further improvements of this approach, in particular, with regard to efficient isolation (such as precipitation, crystallization, or extraction) of the target amine product. This way the emerging route would significantly reduce solvent and energy consumption, resulting in a decrease in the overall PMI value. In the classical route, Steps 1–4 are well-established industrially-used procedures utilizing simple techniques such as distillation and filtration (green flags), while the remaining steps require the use of column chromatography and extraction, leading to red and yellow labels, respectively.

4.3 Evaluation of the green credentials for the synthesis of ranitidine

As in the previous chapter, herein we attempted to compare two main synthetic routes for the production of ranitidine, a drug currently used to treat peptic ulcer and gastroesophageal reflux disease, in terms of greenness. Although both paths start with biomass-derived platform chemicals, namely furfural and 5-(chloromethyl)furfural (CMF), choosing these examples we primarily aimed to emphasize the advantage of using reductive amination transformation in a synthetic sequence over classical organic stoichiometric reactions.

As such, for the comparative analysis of quantitative and qualitative green credentials, the following four-step pathways were selected (Scheme 2). For both routes, the last step, condensation/nucleophilic substitution with *N*-methyl-1-(methylthio)-2-nitroethen-1-amine, is the same, whereas the first three transformations are significantly different. The classical route proceeds through (1) furfural reduction;[250] (2) aminomethylation of furfuryl alcohol by a Mannich-type reaction[251] and (3) nucleophilic substitution with cysteamine.[252] In contrast, the alternative path begins with (a) nucleophilic substitution of the alkyl halide with cysteamine; followed by (b) reductive amination step to convert the aldehyde functionality of CMF to a tertiary amine group and (c) acetyl deprotection.[253]

Data obtained using the CHEM21 green metrics toolkit for both the classical and alternative routes are presented in Scheme 2 (for more details see ESI, Tables S4 and S5†). Although in this particular case neither of the two paths shows significant overall benefits, the alternative path has some promising improvements in individual steps.

Thus, when comparing the mass-based metrics, it can be clearly seen that the use of a reductive amination step in the reaction sequence significantly improves the yield of the entire route. The yield of Step B in the alternative route is 90% compared to 43% in the classical approach, which leads to a fourfold increase in the yield of the target product (68% *vs.* 18%). A similar trend is true for AE: the classical Mannich reaction used in Step 2 is somewhat inferior to reductive amination in terms of atom-efficiency (74% *vs.* 83%). Although looking at other metrics, such as PMI and WU, the alternative route seems to have a clear disadvantage compared to the classical method, showing significantly higher values for these parameters at each individual step, it is worth noting that this process is at the development stage. Therefore, comparison and evaluation of these parameters should be made with caution.

Considering the qualitative parameters, both approaches received relatively equal numbers of red and yellow flags based on the toxicity of the solvent, 'health and safety' considerations, critical elements used, energy consumption, and work-up methods.

Overall, although the comparison of these two approaches to the synthesis of ranitidine is less straightforward than in the previous chapter using the example of *N*-substituted tetrahydro-2-benzazepines, here we have sought to draw the reader's attention to the importance of analyzing each step of the synthesis and its contribution to the overall greenness of the process. The alternative path for the synthesis of ranitidine clearly indicates the benefits of employing atom-economic transformation such as reductive amination in the synthetic sequence. This conclusion becomes more obvious when taking into account the quantitative and qualitative values obtained using the CHEM21 toolkit for each step, as well as cumulative metrics.

4.4 Evaluation of the green credentials for the synthesis of norfenefrine

Norfenefrine is a sympathomimetic pharmaceutical used to treat hypotension regulating blood pressure by acting as a minor neurotransmitter in the brain. In this section, we analyze two approaches to synthesise norfenfrine. The classical pathway[254–258] starts from petrol-based benzene, while the bio-based route[237] involves cardanol as the starting reagent. Data obtained *via* the CHEM21 green metrics toolkit are depicted in Scheme 3 (see ESI, Tables S6 and S7†).

In terms of quantitative green credentials, the bio-based pathway shows a higher overall yield compared to the classical

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pathway (52% *vs.* 17%). It should be noted that the urotropine-mediated amination in Step 5 is particularly limiting as it allows to obtain norfenerine in only 22% yield. In contrast, the aminohydroxylation performed in Step C yields the target drug at 73% yield. A similar trend is observed for RME, where Step C shows a higher efficiency (13.8% *vs.* 7.3%, Table S6†), confirming the advantages of a catalytic amination approach over traditional organic stochiometric reactions. However, the overall RME is relatively low in both routes. For the bio-based pathway, this is largely due to the high solvent usage in synthetic and purification steps. The PMI data, however, highlights a key difference between the two processes: the bio-based route achieves a much lower PMI (6036 g g^{-1} *vs.* 47 588 g g^{-1}) compared to the classical pathway. This is attributed to the fewer reaction steps which exclusively involves catalytic transformations.

As the qualitative parameters are concerned (Scheme 3 and Table S7†) the bio-based route shows a slightly lower amount of red and yellow flags. The classical pathway accounts for three red flags (DCM, $CHCl_3$, 1,4-dioxane) as regards the reaction solvents, while only yellow (2-Me-THF, THF, AcCN) and green labels (water) are observed for the bio-based pathway. However, both pathways have similar disadvantages when considering the solvents used for the work-up procedures. Three red flags arise from each route. As a consequence, 'health & safety' data are similar for both routes. In this regard, petrol-based benzene (H340, H350, H372, H410) is utilized as the starting reagent in Step 1 and as the solvent in Step 4's work-up, while most bio-based route's red flags derive from the use of DCM (H351, H 373) and petroleum ether (H411) during work-up. Only green labels are observed for the reagent use (catalyst) and energy use (RT to 50 °C) utilized in each step of the bio-based pathway. It should be noted that the bio-based approach accounts for two red flags concerning the metals employed since Ru is used in Steps A and B. It is not surprising that the work-up procedures display only red flags for this route, given the extensive use of flash-chromatography protocols, typically employed in lab-scale procedures when low amounts of product need to be isolated. On the other hand, as previously stated, this opens up the way for further improvements to deliver the target products while utilizing less impactful work-up methods.

Overall, it is clear from the processes herein described that catalytic aminohydroxylation helps to reduce the impact of the chemical synthesis of norfenefrine.

However, further optimization is needed in areas such as the use of non-noble catalysts and the development of efficient work-up procedures with non-hazardous, environmentally friendly solvents.

4.5 Evaluation of the green credentials for the synthesis of hexane-1,6-diamine (1,6-HMDA)

Renowned as nylon-6,6, poly(hexamethylene adipamide) is a polymer with widespread applications and significant market value. It is manufactured on an industrial scale through the polycondensation of hexamethylene diamine (1,6-HMDA) and adipic acid.[259,260] Although the actual coupling reaction of these starting materials does not pose any difficulties, the synthesis of both starting materials 1,6-HMDA as well as adipic acid has been subject to scrutiny in terms of environmental impact.

The primary method for obtaining hexamethylene diamine is the hydrocyanation of fossil-based butadiene, followed by hydrogenation of the resulting adiponitrile. Despite its effectiveness, this classical approach suffers from serious limitations, including the petrochemical nature of the starting materials, the high toxicity of reagents (hydrogen cyanide – HCN), as well as the requirement for high temperature and pressure conditions. In the pursuit of transitioning towards a bio-based economy and recognizing the significance of nylon-6,6, extensive research has been dedicated to formulating a more sustainable reaction scheme rooted in renewable resources.[239] This has led to the development of alternative bio-based pathways for HMDA production, starting with high fructose syrup derived from maize and potato-based starch, with 5-(hydroxymethyl)furfural (5-HMF) serving as an intermediate building block.[93,238]

Numerous research groups reported various approaches for the conversion of 5-HMF into the desired HMDA, and these efforts can be categorized into two primary approaches: through the intermediates of 1,6-hexanediol (1,6-HDO) and 2,5-bis(aminomethyl)tetra-hydrofuran (AM-THF).

Route from 5-HMF to 1,6-HDO involves catalytic hydrogenation and hydrodeoxygenation transformations and can be carried out in four different ways: (1) the direct hydrogenation of HMF to 1,6-HDO; (2) a two-step sequence *via* 2,5-THF-dimethanol (THFDM); (3) a three-step synthesis *via* THFDM and 1,2,6-hexanetriol (1,2,6-HT); and (4) a four-step synthesis *via* THFDM, 1,2,6-HT, and tetrahydro-2*H*-pyran-2-ylmethanol (2-THPM). It is worth noting that although one-step, one-pot approaches were realised to directly convert 5-HMF to 1,6-HDO, poor yields of the final product and low selectivity remained a drawback for these protocols.[261,262] In fact, hydrogenolytic THFDM ring opening with the selective formation of 1,6-HDO presents the main challenge in this sequence, making it difficult to overcome in a one-pot process. This issue can be addressed in stepwise processes through a careful design of the catalyst system. For example, employing the RANEY® nickel catalyst 5-HMF is first reduced to THFDM and then further hydrogenated over a Rh–Re/SiO_2 catalyst with the addition of Nafion SAC-13 to the desired 1,6-HDO.[263] The final amination of 1,6-HDO to produce HMDA poses its own set of challenges. Achieving the selective synthesis of a primary α,ω-amine from the corresponding diol is a complex task, given the potential for undesired cyclization and over-alkylation. To overcome these issues, the hydrogen borrowing methodology has proven to be the most efficient. As an example, 1,6-HMDA can be generated through an amination reaction using the Ru-acridine complex as a catalyst within this approach.[264]

An alternative synthetic route to obtain HMDA involves (a) the oxidation of 5-HMF to 2,5-diformylfuran (DFF), (b) reductive amination/hydrogenation of DFF to AM-THF, and subsequent (c) hydrodeoxygenation of the latter to produce the desired

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product 1,6-HMDA. The first step of the sequence, namely selective oxidation or dehydrogenation of the hydroxymethyl group of 5-HMF, is frequently associated with multiple undesired side reactions such as over-oxidation, decarboxylation, ring-opening, and cross-polymerization. As an example, the over-oxidation process could lead to the formation of 5-hydroxymethylfuran-2-carboxylic acid (HMFCA) and furan dicarboxylic acid (FDCA).[265–267] Although dehydrogenation eliminates concerns about over-oxidation, nevertheless, this process being endothermic requires higher temperatures, making side reactions more probable. In the subsequent step, the conversion of DFF to AM-THF also remains a challenge despite recent advancements in reductive amination. To prevent the formation of by-products such as secondary, tertiary, and polymeric amine species resulting from the condensation and/or hydrogenation of the reactive di-aldehyde groups and highly nucleophilic amine groups of the product, highly selective and delicate approaches are required. The final step of this sequence is the opening of the AM-THF molecular ring by reaction over a hydrodeoxygenation catalyst leading to the formation of HMDA.

Adipic acid (ADP), another crucial chemical in the synthesis of nylon-6,6, is predominantly manufactured through a multi-step sequence.[268–271] This involves the hydrogenation of benzene obtained from petroleum to produce cyclohexane, subsequent cyclohexane oxidation to yield a mixture of cyclohexanone and cyclohexanol known as ketone-alcohol oil (KA oil), and further oxidation of KA oil using nitric acid to generate adipic acid.[272] This process, being highly energy inefficient, faces the problems of emission of nitrous oxide (N_2O), a potent greenhouse and ozone-depletion gas, and low efficiency largely attributed to the meager single-pass yield (<10%) of ketone-alcohol oil (KA oil) in the oxidation of cyclohexane.

The production of adipic acid, one of the most important industrial chemicals, through a wasteful energy-inefficient multi-step process involving an aggressive oxidant (HNO_3) has raised many concerns. As a result, over the last decades, significant efforts were devoted to the development of alternative oxidants[269] to enable NO_x free process, and more sustainable routes[273] for the synthesis of adipic acid starting from petrochemical or, ideally, renewable feedstocks, capable of reducing the capital cost investments.[274] Multiple studies on the use of various feedstocks including cyclohexane, phenol, butadiene, and adiponitrile for ADP synthesis have been reported; however, most of these materials are produced from petroleum-derived benzene, leading to a comparable cost structure. Recently, advances in the sustainable preparation of ADP from biomass-based platform molecules, including 5-hydroxymethylfufural, glucose, γ-valerolactone, and phenolic compounds, through biocatalysis, chemocatalysis, and the combination of both, have emerged.[275,276]

A major component of lignocellulosic biomass, cellulose,[277–280] which consists of glucose units connected by β-1,4-glycosidic linkage, has proven to be a promising starting material for the synthesis of adipic acid or adipate esters through catalytic transformations of glucose-derived C6 dicarboxylic acids such as 2,5-furandicarboxylic acid (FDCA)[281,282] and mucic acid.[283–285] However, despite the effectiveness of these methodologies, the production of these acids is not straightforward, demanding multiple chemical reactions[277,279] or biological fermentation processes.[284,285] As an attempt to overcome these issues, very recently, a fascinating two-step transformation of cellulose-derived glucose into adipic acid *via* glucaric acid was reported.[286] In this approach, glucose is first oxidized into glucaric acid over a Pt/CNT catalyst, which undergoes deoxydehydration reaction to form adipic acid after the removal of four OH groups in the presence of a bifunctional Pd–ReO_x/AC catalyst.

5-Hydroxymethylfufural (5-HMF) is another renewable platform molecule that could be extracted from cellulose and used as a feedstock for ADP production.[93] As an example, catalytic hydrolysis of lignocellulose to HMF under acidic conditions (H_2SO_4), followed by oxidative conversion to 2,5-furandicarboxylic acid (FDCA), and a subsequent deoxygenation reaction yields the final product, ADP. The alternative path is based on catalytic hydrogenation of HMF to 1,6-hexanediol (1,6-HD) followed by biocatalytic oxidation of two hydroxy groups of 1,6-HD to carboxylic acid groups to obtain ADP. It is worth noting that the first step of the latter route poses a significant challenge as identifying effective catalysts capable of simultaneously saturating the C=C bond and facilitating the ring opening of cyclic ethers proves to be difficult.

Besides glucose and 5-hydroxymethylfufural, γ-valerolactone (GVL)[287] and lignin-derived phenolic compounds[288] represent other renewable starting materials with great potential for the synthesis of ADP. It is noteworthy that γ-valerolactone (GVL), in turn, can be produced by hydrogenating levulinic acid (LA), which is obtained through the acid-catalysed hydrolysis of biomass feedstocks.[289] Thus, the general catalytic approach for the synthesis of ADP from GVL includes (a) GVL acid-catalysed hydrolysis and reactive distillation to form pentenoic acid isomers (PEAs) and (b) the carbonylation of PEAs to ADP.[290,291] As another contrasting example, an integrated strategy for the biochemical conversion of lignin-derived monomers to adipic acid was recently disclosed.[284] In this process, the oxidative ring-opening reactions of phenolic compounds catalysed by biocatalysts (*Pseudomonas putida* KT2440) obtain muconate, which is further hydrogenated to ADP over a Pd/C catalyst.[292,293]

4.5.1 Comparative analysis: discussion of the obtained results. For comparative analysis in this chapter, we chose three different pathways for HMDA synthesis. In this particular case, we intentionally chose two routes based on previously discussed atom-economic transformations such as hydrogen borrowing and reductive amination. Here we aimed to compare these routes with each other and with the commercial one, identifying the advantages and drawbacks of each step and each approach. As such, the following routes were thoroughly analysed using CHEM21 toolkit: (1) butadiene → adiponitrile → HMDA;[294–296] (2) 5-HMF → THFDM → 1,6-HDO → HMDA;[263,264] (3) 5-HMF → DFF → AMF → AM-THF → HMDA.[297–300] The values of quantitative and qualitative metrics for commercial and sustainable approaches are summarised in Scheme 4 and Tables S8 and S9 (see ESI for more details†).

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Based on the obtained data, it is clear that bio-based approaches have the potential to be considered as a future replacement for the current industrial process after appropriate optimization. Considering that bio-based pathways are at the discovery level (first pass CHEM21 green metrics toolkit), it is noteworthy that the yield of the target HMDA is almost three times higher for bio-based approaches 1 and 2 than for commercial process (71% and 79% *vs.* 23%, respectively). Although the PMI and RME values are still considerably more advantageous for the industrial process, careful optimization of the isolation procedure as well as catalyst/solvent recovery at pilot and industrial scales might significantly improve current values for the bio-based routes. The benefits of bio-based approaches become more apparent when comparing the qualitative parameters of commercial and sustainable routes, as evidenced by fewer red flags. Both bio-based pathways (1) utilize renewable feedstocks such as cellulose-derived 5-HMF instead of petroleum-based butadiene; (2) avoid the use of toxic and hazardous materials and solvents such as hydrogen cyanide and benzene; (3) require less energy consumption – reaction temperatures at most stages are below the boiling point of the solvent/between 0 and 70 °C.

When comparing bio-based pathways with each other (Table S8†), the reductive amination-based route (bio-based approach 2) despite the increased number of steps (4 steps *vs.* 3 steps) leads to a higher overall yield (79% *vs.* 71%). The opposite is true for the PMI: fewer reaction steps and efficient work-up procedures (distillation) for hydrogen-borrowing-based approach (bio-based approach 1) result in reduced waste generation; thus, PMI Tot for bio-based approach 1 is six times less than for Bio-based approach 2 (144 g g^{-1} *vs.* 876 g g^{-1}). In fact, the reductive amination step (Step B in Bio-based approach 2) negatively contributed to the overall PMI value due to the inefficient isolation procedure and the uneconomic amount of the solvent utilized. While AE values are comparable for both approaches (86% *vs.* 88%), RME for Step III, bio-based approach 1 is significantly higher than for Step B, bio-based approach 2 (56% *vs.* 9%). This parameter, considering the stoichiometry of the reaction, clearly indicates the excess of the reactants used in the reductive amination step, which negatively affects the overall RME of the entire process. Overall, despite some minor differences in values of quantitative and qualitative parameters, both atom-economic routes have proven to be effective for introducing amine functionality into the target product, 1,6-HMDA.

In their invaluable contribution, Pera-Titus and coworkers have presented[239] an economic and LCA comparative study which revealed that the commercial process for HMDA synthesis is more cost-effective and environmentally favourable than existing bio-based alternatives, mainly due to costs related to feedstock sourcing and energy demands (see section 4.1). This points out the need for more efficient biorefinery approaches. Nonetheless, the green credentials calculated here give an immediate comparison of the synthetic routes and sustainability of laboratory processes, decoupled from feedstock sourcing.

5. Conclusions

The transition to a circular, bio-based economy requires the development of novel catalytic approaches, which enable alternative pathways to the production of industrially important chemicals from renewable carbonaceous feedstocks;[301] chief among these are amines. Due to the structural mismatch between renewable and fossil-based feedstocks, catalyst development should embrace the inherent structural features of renewable starting materials to allow markedly more sustainable and efficient routes to amines.[9] This is important to ensure the competitiveness of the newly developed routes since the established petrochemical production pathways have been optimized – literally – for decades, to maximize performance. However, fossil-based pathways to industrial products display a fundamental drawback: they were developed with the sole focus on performance without consideration of principles of sustainability and green chemistry as design criteria.[302] Moreover, the distinctly simple nature of petrochemical building blocks typically leads to multi-step or harsh conditions to access amines. Therefore, any new bio-based route should aim for higher step, atom, and energy efficiency and sustainability from renewable platform chemical to product to allow for competitive benefits. However, it is not sufficient to simply state "The new route is 'greener' because it comes from renewables". Any newly developed route should be closely scrutinized in terms of reaction performance metrics, and green metrics to understand future substitution potential and possible industrial importance.[303,304]

Herein, we illustrate the application of green metrics incorporated in the CHEM21 toolkit for a first basis comparison of novel (renewables-based) and classical (petrol-based) pathways through four selected case studies. The first case study considers the synthesis of *N*-substituted tetrahydro-2-benzazepines, compounds with pharmaceutical importance, one starting from petrol-based benzene through classical synthesis, and one from lignin-derived dihydroconiferyl alcohol *via* the hydrogen borrowing methodology. It can be clearly seen that the classical route requires 13 steps to obtain the targeted compound, while the new pathway delivers the final product in only 3 steps from woody biomass. The advantages of this latter approach in terms of yield, biomass utilization and energy efficiency, are immediately apparent.

A second example considers the synthesis of ranitidine from biomass, namely from furfural and 5-(chloromethyl)furfural (CMF) important cellulose-derived platform chemicals, involving a reductive amination approach and stoichiometric classical transformations, respectively. This case demonstrates that simply being bio-based is not enough to achieve a marked difference compared to a well-optimized classical route. The advantages and disadvantages of both routes are elaborated, and possibilities for improvement of the new route are proposed.

As a third example, the synthesis of norfenefrine is illustrated *via* a comparison between the classical pathway starting from benzene and a bio-based alternative route starting from cardanol. This example highlights the advantages of catalytic

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processes over traditional organic reactions in terms of overall yield and process mass intensity (PMI). However, it also shows the need to optimize work-up procedures for synthetic procedures from renewables. These are often performed at the lab scale and require high solvent loads for tedious work-ups, such as chromatography columns.

Finally, very important nylon-6,6 monomers were illustrated, namely 1,6-HMDA and adipic acid. The importance of this example lies in its significant market value, nylon-6,6 being produced on a scale of >8 million tons a year,[305,306] and its classical production is environmentally largely problematic. Therefore, the development of a sustainable and preferably bio-based pathway will be of major significance. Here our analysis outlines several promising possibilities for the production of nylon-6,6, starting from renewable resources. In particular, we have cross-compared two alternative approaches based on cellulose-derived 5-HMF and with the current industrial process based on petroleum-derived butadiene. Given the quantitative and qualitative values of the key green metrics, it was concluded that bio-based routes could be considered a viable alternative to the current industrial process, potentially offering a safer and energy-efficient approach with a higher overall yield after appropriate optimization. Comparison of atom-economic routes with each other, namely reductive amination and 'hydrogen borrowing', revealed that these approaches are equally effective in introducing amine functionality into the 1,6-HMDA structure, as expected.

Overall, in this contribution we have demonstrated the development of 'waste-free' catalytic methods for the selective amination of biomass-derived platform chemicals, to furnish industrially important amines. A detailed description of available catalytic systems was presented for reductive amination and alcohol-to-amine transformations *via* the hydrogen borrowing methodology, as applied to substrates that (potentially) originate from renewable resources. While many of these fundamental research results represent impressive scientific progress, the reported processes are typically at lower TRL levels, where process intensification has not yet been performed. Nonetheless, it is expected that such developments will happen towards integrating such methods into industrial processes.

In this review article, our focus was on the demonstration and use of numerical and qualitative green chemistry metrics, included in the CHEM21 toolkit, as an important first step towards the comparison of fossil-based and renewables-based routes, at the reaction and process level. Of course, this approach alone is not sufficient to derive final conclusions about the specific routes and processes and a more elaborate life cycle analysis will be necessary to estimate the overall sustainability of the processes in question. Full life cycle analysis, cradle to grave, will consider potential challenges with regard to feedstock sourcing, global warming potential as well as the fate of the final products.[32,33] While fossil-based pathways already possess a well-established raw material supply chain, the non-renewable nature of petroleum-based starting materials will negatively impact the carbon footprint of related products.[239,243,293] On the other hand, the processing, sourcing, and availability of specific renewable resources are ongoing developments and success will depend on future overall progress in the development of biorefinery approaches at scale. While several frontrunners have emerged over the past decade, future research and development should allow efficient access to specific platform chemicals at scale and competitive price points.[307,308] Other factors, such as environmental impact related to land use, production capacity, and availability of diverse renewable feedstocks within planetary boundaries, will also have an influence on overall sustainability.[309–311]

It is our strong conviction that progress toward a circular and bio-based economy depends on our capacity to deliver elegant fundamental scientific solutions. The relatively simple metrics discussed in the review provide easy-to-use tools in the hands of laboratory chemists to evaluate, compare, and scrutinize their fundamental innovations early in the discovery process. Such early assessment may guide catalyst design and method development, and illuminate immediate advantages of a newly developed synthetic route, which will ultimately provide a road ahead for future industrial development.

Author contributions

Conceptualization: AMA, KB; visualization: AMA; project administration: KB; funding acquisition: KB; writing – original draft: AMA, ND, JO, RS, KB; writing – review & editing: AMA, ND, JO, RS, KB.

Data availability

The data supporting this article have been included as part of the ESI.†

A separate dataset detailing specific calculations has been provided as additional dataset.

This review does not contain specific experimental data.

Conflicts of interest

There are no conflicts to declare.

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