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Published in:
Green Chemistry

Link to article, DOI:
[10.1039/d0gc01869d](https://doi.org/10.1039/d0gc01869d)

Publication date:
2020

Document Version
Peer reviewed version

[Link back to DTU Orbit](#)

Citation (APA):
He, J., Chen, L., Liu, S., Song, K., Yang, S., & Riisager, A. (2020). Sustainable access to renewable N-containing chemicals from reductive amination of biomass-derived platform compounds. *Green Chemistry*, 22(20), 6714-6747. <https://doi.org/10.1039/d0gc01869d>

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Green Chemistry

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Sustainable access to renewable N-containing chemicals from reductive amination of biomass-derived platform compounds

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Abstract

Nitrogen-containing compounds are pivotal building blocks with extensive application in the manufacture of pharmaceuticals, polymer materials, agrochemicals and organic synthesis. The sustainable production of nitrogen-containing compounds from renewable biomass derivatives has attracted much attention with particular interest on the reductive amination of bio-based platform molecules. Herein, an overview on the latest advances in the reductive amination of bio-based platform molecules is provided. Emphasis is primarily concentrated upon several renowned bio-based platform molecules, such as furfural, 5-hydroxymethylfurfural, levulinic acid and lignin model monomers. In addition, progress with state-of-the-art catalysts of different catalytic system based on different reductants including gaseous H_2 , formic acid, $NaBH_4$ and hydrosilane are systematically summarized and discussed. Moreover, structure-reactivity relationships, reaction pathway/mechanism and durability as well as generality of catalysts are also highlighted.

Keywords: Nitrogen-containing compounds; reductive amination; biomass; platform molecules; fine chemicals

1 Introduction

Interest in sustainable chemistry research is continuously growing towards producing valuable chemicals and fuels from renewable resources given the expected shortage of fossil-based resources [1-3]. In this context, lignocellulosic biomass stands out as a promising renewable carbon source for chemical industry as it is associated with abundant reserves, eco-friendliness and worldwide distribution [4-6]. Lignocellulosic biomass is predominantly constituted of cellulose, hemicelluloses and lignin, and the transformation of these three biopolymers into value-added chemicals and bio-fuels is currently the theme of biomass valorisation [7-9]. Technically, the transformation of the three biopolymers into small organic intermediates, namely platform molecules, is an essential step to progress towards the synthesis fine chemicals, drop-in bio-fuels and biodegradable materials [10-12]. At present, a variety of platform molecules such as 5-hydroxymethylfurfural, furfural, levulinic acid, lactic acid and phenol can efficiently be obtained from lignocellulosic biomass (Figure 1), and those platform molecules can subsequently serve as substitutes for fossil-based feedstock in the manufacture of fine chemicals and bio-fuels [13-15].

Nitrogen-containing compounds are extensively found in diverse bioactive molecules including peptides, alkaloids, nucleic acids and other natural products, as well as widely present in a variety of commonly used pharmaceuticals [16-18]. From a chemical point of view, nitrogen-containing compounds are a pivotal kind of building blocks with extensive application in the synthesis of pharmaceuticals, food additives, detergents, polymer materials and agrochemicals [19-20]. Traditionally, the synthesis of nitrogen-containing compounds has primarily relied on fossil-based feedstock, rendering more sustainable synthesis from renewable resources highly desirable [21]. Biomass and its derivatives represent such promising renewable starting materials, and various efforts have focused upon its utilisation for the sustainable production of nitrogen-containing compounds [22]. This includes several elegant strategies such as, e.g. conversion of nitrogen-containing carbohydrates [23], catalytic fast pyrolysis of

carbohydrates in ammonia [24, 25] and reductive amination of biomass-derived platform molecules [26, 27]. The advantages associated to the latter strategy of reductive amination include high selectivity towards targeted nitrogen-containing compounds, operation under mild conditions and diversity in product compounds [28]. Coupled with the remarkable achievements in synthesis of platform molecules from biomass, reductive amination of bio-based platform molecules has accordingly received particular interest in recent years.

Figure 1 Diagram of representative nitrogen-containing compounds and platform molecules derived from biomass

Many nitrogen-containing compounds are successfully assessable from bio-based platform molecules via the reductive amination approach (Figure 1). In general, the

approach comprises cascade reactions from the platform molecules, which after conversion to imine intermediates followed by subsequent reduction are converted into the target nitrogen-containing compounds [29-33]. Noteworthy, with regard to specific molecules (*e.g.*, bio-based alcohols or levulinic acid), dehydrogenation or cyclisation is also included in the tandem reaction [34-36]. Normally, both acidic sites and metallic sites are required for the cascade reaction, although the formation of imine intermediates without any catalyst is also reported [37]. In addition, the choice of appropriate reductants is crucial for the reductive amination as an essential step in the cascade reaction. Several reductants including gaseous H_2 , formic acid ($HCOOH$), sodium borohydride ($NaBH_4$) and hydrosilane ($HSiR_3$) have already been applied successfully for reductive amination of bio-based platform molecules and new reductants are still frequently being reported.

In the present review, the latest studies on the synthesis of nitrogen-containing compounds from bio-based platform molecules, primarily focusing on furfural, 5-hydroxymethylfurfural, levulinic acid and lignin model monomers, are systematically summarized and discussed. Emphasis are directed upon the state-of-the-art catalysts applied in the different catalytic systems relying on different reductants, structure-reactivity relationships, corresponding reaction pathways/mechanisms and durability as well as versatility of the catalyst systems. Moreover, some tentative suggestions are presented for future studies aiming towards accelerating industrial implementation of syntheses of nitrogen-containing compounds from reductive amination of bio-based platform molecules.

2 Reductive amination of furfural

Furfural is accessible from acid-catalyzed tandem hydrolysis-dehydration of hemicellulose or from acid-facilitated transformation of cellulose-derived hexoses [38-40], and affords sustainable access to a variety of liquid bio-fuels and valuable chemicals via different upgrading strategies such as, *e.g.* hydrogenation, oxidation,

amination and aldol condensation [41-45]. Amongst the strategies, the reductive amination of furfural with ammonia or primary amines is a versatile and elegant way to synthesize valuable amines, including furfurylamine and its derivatives, which have a large spectrum of applications in the manufacture of pharmaceuticals, pesticides, synthetic resins and useful agrochemicals [46]. Reductive amination of furfural with amines (including ammonia) is a cascade reaction consisting of the formation of imines and sequential hydrogenation to yield furfurylamine or its derivatives (Scheme 1) [46]. A pivotal step in the cascade reaction is the selectivity hydrogenation of *in situ* formed imines to amines owing to the presence of competitive side reaction (*i.e.*, the hydrogenation of furfural) [47]. Therefore, development of effective catalysts along with choosing appropriate reductants is crucial for the reductive amination of furfural. The reductive amination of furfural is herein discussed on the basis of applied reductants.

2.1 Gaseous hydrogen as reductant

Hydrogen gas, especially pressurized hydrogen gas, is a frequently used reductant in the hydrogenation of unsaturated bonds in organic synthesis as it is easy to activate on various metal surfaces. Pressurized H₂ gas has also succeeded in serving as reductant for the reductive amination of furfural, where many metal-based catalysts have been exploited.

2.1.1 Noble metal-based catalysts

Ammonia is a cheap and easily available nitrogen source, which has received much attention in the field of reductive amination. Many noble metal-based catalysts have been developed for the reductive amination of furfural using ammonia as nitrogen source and using H₂ gas as reductant as compiled in Table 1 [47-53]. By using homogeneous RuCl₂(PPh₃)₃ as catalyst, Jagadeesh *et al.* performed the reductive amination of furfural with ammonia, giving 85% yield of furfurylamine under the conditions of 130 °C, 24 h and 4 MPa H₂ (entry 1, Table 1) [48]. A key to success with the RuCl₂(PPh₃)₃ catalyst was the formation of Ru-hydride species (*i.e.*,

[$\text{RuH}_2(\text{PPh}_3)_3$] or [$\text{RuHCl}(\text{PPh}_3)_3$] in the reaction mixture as revealed by *in situ* NMR studies, which served as active species reacting with formed furfurylimine to selectively facilitate generation of furfurylamine. However, the $\text{RuCl}_2(\text{PPh}_3)_3$ catalyst encountered difficulties with separation and reuse, which greatly plagued its practical applications. Exploitation of heterogeneous catalysts for the reductive amination of furfural has recently received great interest. Ebitani and co-workers reported in 2016 that poly(*N*-vinyl-2-pyrrolidone)-stabilized Ru-supported hydroxyapatite (Ru-PVP/HAP) catalyst facilitated the reductive amination of furfural in ammonia aqueous solution smoothly at 100 °C, affording 60% yield of furfurylamine at 0.4 MPa of H_2 (entry 2, Table 1) [49]. They claimed that metallic Ru clusters with mean diameter of ~1.7 nm were responsible for the moderate catalytic performance of Ru-PVP/HAP after scrutinizing Ru-PVP/HAP catalyst through *X*-ray absorption spectroscopy and transmission electron microscope measurements. The reusability of Ru-PVP/HAP was, however not investigated.

Scheme 1 Reaction pathway for the reductive amination of furfural with ammonia or aniline [50, 53]

The low yield of furfurylamine with the heterogeneous Ru-PVP/HAP catalyst initiated considerable research optimizing the reductive amination of furfural with

ammonia via heterogeneous catalysis. As illustrated in Scheme 1, unfavorable side reactions include the formation of difurfurylamine and furfuryl alcohol competing with the formation of furfurylamine rendering the selectivity synthesis of furfurylamine challenging. The challenge of the selective formation of furfurylamine was further corroborated by Hara and co-workers [50] by virtue of density functional theory (DFT) calculations, where they found the formation of difurfurylamine and furfuryl alcohol was more thermodynamically favorable relative to the formation of furfurylamine. Ru nanoparticles supported on Nb₂O₅, SiO₂ and TiO₂ was discovered to be effective for the reductive amination of furfural with ammonia by screening various oxide supports (*e.g.*, Nb₂O₅, SiO₂, TiO₂, Al₂O₃, ZrO₂ and MgO), leading to 89, 84 and 72% yield of furfurylamine, respectively, at 90 °C and 4 MPa H₂ (entries 3-5, Table 1) [50]. Superior catalytic behavior of Ru/Nb₂O₅ was attributed to the low electron density of Ru together with the positive charges on the Nb₂O₅ surface compared to Ru/SiO₂ and Ru/TiO₂ as demonstrated by CO-adsorbed Fourier transformed infrared spectroscopy tests. Moreover, the activity of Ru/Nb₂O₅ was nearly maintained without noticeable decrease in four consecutive reaction runs. Coincidentally, Rh/Al₂O₃ was also confirmed to be active for the reductive amination of furfural and ammonia, contributing to 91.5% yield towards furfurylamine (entry 6, Table 1).

In an effort to improve the yield of furfurylamine, Ru nanoparticles endowing flat-shaped pristine fcc as well as abundant atomically active {111} facets [51] and Ru/Nb₂O₅·nH₂O-300 catalyst [52] have been successively developed for catalyzing the reductive amination of furfural with ammonia (entries 7-8, Table 1). Noteworthy, Ru/Nb₂O₅·nH₂O-300 showed excellent catalytic performance providing 89% yield of furfurylamine under mild reaction conditions (70 °C), which resulted from the large amount of acid sites within Nb₂O₅·nH₂O-300. It was proposed, that acid sites exerted a vital role in the activation of furfurylimine and in turn facilitated the formation of furfurylamine [52]. A positive influence of acid sites on the reductive amination of furfural was further validated by Martínez *et al.* [53] using sulfonic

acid-functionalized silica support to prepare Au/SiO₂-SO₃H, Ir/SiO₂-SO₃H and Pt/SiO₂-SO₃H catalysts for the reductive amination of furfural with aniline. Here, the as-prepared catalysts enabled the reductive amination to proceed successfully at very low reaction temperature (*i.e.*, room temperature) (entries 9-11, Table 1). The authors demonstrated that the synergistic effect of acid sites and metal sites was crucial for the reductive amination of furfural with aniline, where the formation of imine was facilitated by acid sites while the reduction of (*E*)-1-(furan-2-yl)-*N*-phenylmethanimine to yield *N*-(furan-2-ylmethyl)aniline was promoted over metal sites.

Table 1 Reductive amination of furfural with ammonia or aniline over noble metal-based catalysts

Entry	Catalyst	Nitrogen source	P _{H2} (MPa)	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)	Ref.
1	RuCl ₂ (PPh ₃) ₃	NH ₃ (0.5-0.7 MPa)	4	130	24	-	85 ^b	[48]
2	Ru-PVP/HAP	NH ₃ aqueous solution (25 %)	0.4	100	2	-	60 ^b	[49]
3	Ru/Nb ₂ O ₅	NH ₃ (16 equiv.) ^a	4	90	4	-	89 ^b	[50]
4	Ru/SiO ₂	NH ₃ (16 equiv.) ^a	4	90	4	-	84 ^b	[50]
5	Ru/TiO ₂	NH ₃ (16 equiv.) ^a	4	90	4	-	72 ^b	[50]
6	Rh/Al ₂ O ₃	NH ₃ (33 equiv.) ^a	2	80	2	100	91.5 ^b	[47]
7	Ru-NP	NH ₃ (16 equiv.) ^a	2	90	2	-	99 ^b	[51]
8	Ru/Nb ₂ O ₅ ·nH ₂ O-300	NH ₃ methanol solution (1.6 M)	4	70	4	>99	89 ^b	[52]
9	Au/SiO ₂ -SO ₃ H	Aniline	5	r.t.	8	48	3 ^c	[53]
10	Ir/SiO ₂ -SO ₃ H	Aniline	5	r.t.	8	58	19 ^c	[53]
11	Pt/SiO ₂ -SO ₃ H	Aniline	5	r.t.	8	71	21 ^c	[53]

^a Molar equivalent relative to furfural.

^b Yield of furfurylamine.

^c Yield of *N*-(furan-2-ylmethyl)aniline.

2.1.2 Non-noble metal-based catalysts

Despite the as-above described excellent activity of noble metal-based catalysts, the expensive and scarcity of these metals possesses a negative effect on the production cost, which hampers their large-scale industrial application. Hence, unsurprisingly the

study for the development of low-cost and abundant non-noble metal-based catalysts for the reductive amination of furfural has been performed [54-57]. Xu and co-workers [54] reported that both commercial Raney Ni and Raney Co enabled the reductive amination of furfural with ammonia to proceed well (entries 1-2, Table 2), however, higher selectivity towards furfurylamine was observed for Raney Co compared to Raney Ni. The inferior activity of Raney Ni in terms of furfurylamine yield was ascribed to Raney Ni easily promoting the hydrogenation of the furan ring to produce tetrahydrofurfurylamine (24.3% yield). In addition, the authors discovered that the formation of primary amine (*i.e.*, furfurylamine) or secondary amine (*i.e.*, difurfurylamine) depended on the transformation of the imine intermediate (namely *N*-furfurylidenefurfurylamine, derived from the reaction of furfurylamine and furfural), where the hydrogenolysis of *N*-furfurylidenefurfurylamine resulted in the formation of furfurylamine but difurfurylamine was generated from the hydrogenation of *N*-furfurylidenefurfurylamine (Scheme 2a). The superior performance of Raney Co benefited from the catalysts facilitated hydrogenolysis of *N*-furfurylidenefurfurylamine. Recently, Varma *et al.* [55] prepared a magnetic $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Ni}$ catalyst with core-shell structure and used it for catalyzing the reductive amination of furfural in ammonia aqueous solutions. Up to 100% yield of furfurylamine was attained at 115 °C when heated by microwave irradiation for 2 h with 2.0 MPa H_2 (entry 3, table 2). Nevertheless, the yield of furfurylamine decreased to 73% when the reaction was conducted using conventional heating, demonstrating that microwave-assisted heating had a positive effect on the promotion of the furfurylamine production. High stability of the $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Ni}$ catalyst in six consecutive experiments was found due to the core-shell structure, as evident from characterisation tests of fresh and used catalysts. Furthermore, due to its magnetic property the $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-Ni}$ catalyst was facilely separated from the reaction mixture with the help of an external magnet, demonstrating salient time-saving and energy-efficient reaction advantages.

Scheme 2 Schematic diagram for the (a) hydrogenolysis or hydrogenation of the intermediate into primary amine (furfurylamine) or secondary amine (difurfurylamine) [54], (b) Diagram for the reductive amination of furfural with different amines [57]

The reductive amination of furfural with aniline in the presence of non-noble metal-based catalysts was also reported. For example, a combination with $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and EDTA-Na_2 resulted in the formation of Fe(II)/EDTA complexes, which served as active species contributing to 72% yield of *N*-(furan-2-ylmethyl)aniline under reaction conditions of 150 °C, 12 h and 2.76 MPa H_2 (entry 4, Table 2) [56]. Additionally, the reductive amination of furfural with other nitrogen-containing compounds, such as *e.g.*, aminopropanol, glycine and β -alanine, proceeded well in the presence of carbonized filter paper-supported FeNi alloy, giving rise to 50-90% yields of the corresponding target compounds (Scheme 2b) [57].

Table 2 Reductive amination of furfural with ammonia or aniline over non-noble metal-based catalysts

Entry	Catalyst	Nitrogen source	P _{H2} (MPa)	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)	Ref.
1	Raney Ni	NH ₃ (0.1 MPa)	1.0	120	2	100	65.1 ^a	[54]
2	Raney Co	NH ₃ (0.1 MPa)	1.0	120	2	100	98.9 ^a	[54]
3	Fe ₃ O ₄ @SiO ₂ -Ni	NH ₃ aqueous sol. (25 wt%)	2.0	115 ^b	3	100	100 ^a	[55]
4	FeSO ₄ ·7H ₂ O + EDTA-Na ₂	Aniline	2.76	150	12	-	72 ^c	[56]

^a The yield of furfurylamine.

^b Heating with microwave irradiation.

^c The yield of *N*-(furan-2-ylmethyl)aniline

2.2 Using formic acid as reductant

Formic acid is receiving more attention in the domain of transfer hydrogenation as a nontoxic, high-volumetric hydrogen density, easily handled and readily biodegradable liquid hydrogen source [58, 59]. Combined with sustainable production of formic acid from hydrolysis or oxidation of biomass derivatives [60, 61], this renders employment of formic acid as reductant quite attractive. Accordingly, effort have also been performed in recent years on adopting formic acid as reductant for the reductive amination of carbonyl compounds, including furfural [62-64].

Cao and co-workers conducted the pioneering work of coupling the reduction of nitrobenzene and reductive amination of furfural using formic acid as reductant [65]. By screening different carriers including ZrO₂, Al₂O₃, CeO₂, TiO₂ and activated carbon, the authors found that Au loaded on TiO₂ could catalyze efficiently the reductive amination. Particularly, among TiO₂-R (single-phase rutile), TiO₂-A (single-phase anatase) and TiO₂-P25 (biphasic nanocrystalline titania, Evonik P25), the former was observed to be the best carrier for loading Au. Interestingly, Au/TiO₂-R was able to efficiently catalyze the reductive amination of furfural and nitrobenzene using formic acid as reductant with 93% yield of *N*-(furan-2-ylmethyl)aniline under mild reaction conditions of 80 °C and 4 h [65]. The authors claimed that the superior catalytic activity of Au/TiO₂-R was a coalescence of

TiO₂-R endowing mild acid/base sites and Au entailing appropriate transfer hydrogenation activity. As presented in Scheme 3a, the synthesis of *N*-(furan-2-ylmethyl)aniline from furfural and nitrobenzene is a tandem reaction involving the reduction of nitrobenzene to aniline and successive reductive amination of furfural with *in situ* formed aniline to yield *N*-(furan-2-ylmethyl)aniline [65].

Another recent example of using formic acid as reductant for reductive amination of furfural was reported by Smith Jr. *et al.* in 2019 [66]. The authors discovered that the reductive amination of furfural by means of using formamide as nitrogen source, proceeded successfully with Cs₂CO₃ in methanol at 60 °C (heated by oil bath), affording as high as 94% yield of furfurylamine with a reaction time of 1 h. In contrast to the previously reported reaction pathway for the reductive amination of furfural (probably comprising condensation of furfural with ammonia to give imine and successive hydrogenation of imine to form furfurylamine), the authors demonstrated that the synthesis of furfurylamine from furfural and formamide in their work proceeded by the sequential reactions of addition, dehydration, hydrogenation and decarbonylation (Scheme 3b) [66].

Scheme 3 (a) Reductive amination of furfural with nitrobenzene over Au/TO₂-R using formic acid as reductant [65], (b) Reductive amination of furfural with formamide using formic acid as reductant [66]

2.3 Using hydrosilane as reductant

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DOI: 10.1039/D0GC01869D

Hydrosilane obtained from waste residues of the silicon industry is frequently used as cheap, readily available and safe reductant [67-70], and it is particularly attractive to employ hydrosilane as reductant for reductive amination of carbonyl compounds [71]. The use of triethylsilane as reductant for the reductive amination of furfural with diphenylamine was studied by Nakada *et al.* with a homogeneous catalytic system based on BiCl₃ [72]. The targeted product, *N*-(furan-2-ylmethyl)-*N*-phenylaniline, was achieved in 56% yield at room temperature after 22 h reaction (entry 1, Table 3). The difficulty in separation of the product and the catalyst from the homogeneous system limited its industrial application to some extent.

The reductive amination of furfural using triethylsilane as reductant over heterogeneous catalyst was pioneered by Mirza-Aghayan and co-workers [73], where the yield of *N*-(furan-2-ylmethyl)aniline reached up to 80% in the presence of Pd/C at room temperature after only 1 h (entry 2, Table 3). The work presented no recyclability of the Pd/C catalyst, albeit the established heterogeneous catalytic system exhibited a broad substrate scope for reductive amination of various carbonyl compounds. Thus, exploitation of effective and reusable heterogeneous catalysts for reductive amination of furfural using hydrosilane as reductant is continuously drawing attention. In this context, a Bentonite-gold nanohybrid catalyst was determined to be not only efficient for the reductive amination of furfural with aniline (92% yield of target product) but also durable as it preserved its intrinsic activity in five consecutive reaction runs, which encouraged the authors to explore the possible reaction mechanism (Scheme 4a) [74]. They claimed that the reaction initially involved condensation of furfural with aniline to form the imine, while phenyldimethylsilane was simultaneously activated by Au nanoparticles through the oxidative breakage of the Si-H bond. Subsequently, the formed imine was reduced by the activated silane species to generate *N*-silylated amine, which then underwent hydrolysis to yield *N*-(furan-2-ylmethyl)aniline accompanying by the formation of silanol [74]. Coincidentally, Au nanoparticles immobilized onto mesoporous hybrid amine-based

APTES@SBA was also found to be effective for facilitating the reductive amination of furfural with aniline as reported by Pericàs *et al.* [75], furnishing 76% yield of the target product with phenyldimethylsilane as reductant (entry 4, Table 3).

Table 3 Reductive amination of furfural with using hydrosilane as reductant

Entry	Catalyst	Nitrogen source	Hydrosilane	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	BiCl ₃	Diphenyl-amine	Triethylsilane	r.t.	22	56 ^a	[72]
2	Pd/C	Aniline	Triethylsilane	r.t.	1.0	80 ^b	[73]
3	Bentonite-gold nanohybrid	Aniline	Phenyldi-methylsilane	r.t.	2.0	92 ^b	[74]
4	Au@APTES@SBA	Aniline	Phenyldi-methylsilane	r.t.	2.0	76 ^b	[75]
5	HReO ₄	Aniline	Phenyldi-methylsilane	140	1.0	73 ^b	[76]

^a The yield of *N*-(furan-2-ylmethyl)-*N*-phenylaniline.

^b The yield of *N*-(furan-2-ylmethyl)aniline.

Coupling the dehydration of xylose into furfural and reductive amination of furfural in one-pot constitutes an elegant and attractive route towards the synthesis of nitrogen-containing compounds, because the synthetic procedure circumvents separation and purification of intermediates (*i.e.*, furfural). Pioneering work with xylose as starting material for the synthesis of *N*-(furan-2-ylmethyl)aniline was done by Fernandes and co-workers [76] using HReO₄ catalyst. The one-pot synthesis could be realized by virtue of adopting two steps strategies (Scheme 4b); the dehydration of xylose into furfural firstly proceeded at 140 °C for 2 h, where after cooling to room temperature and addition of phenyldimethylsilane and aniline was reacted at 140 °C for 1 h. Finally, as high as 73% yield of *N*-(furan-2-ylmethyl)aniline was attained in the one-pot two-step process (entry 5, Table 3).

Scheme 4 (a) Plausible reaction mechanism for reductive amination of furfural with aniline over Bentonite-gold nanohybrid [74], (b) Transformation of xylose into *N*-(furan-2-ylmethyl)aniline over HReO₄ with one-pot two step method [76]

2.4 Using sodium borohydride or alcohol as reductant

Sodium borohydride is a common low-cost and environmental friendly reductant in organic synthesis [77, 78]. The employment of NaBH₄ as reductant for the reductive amination has been verified to be feasible [79, 80]. For example, Cho *et al.* reported that the reductive amination of furfural with aniline in the presence of NaBH₄ took place smoothly with the assistance of boric acid activator, providing 97% yield of *N*-(furan-2-ylmethyl)aniline at room temperature within only ten minutes [81].

Beside gaseous H₂, formic acid, hydrosilane and NaBH₄, alcohol is another popular reductant in organic synthesis owing to its dual role of hydrogen source and reaction solvent [82, 83]. Actually, the transfer hydrogenation methodology based on using alcohol as hydrogen source is very prevalent in biomass valorisation [84-86]. However, studies regarding reductive amination of furfural using alcohol as reductant are very limited and so far only a few reports are available despite the reaction deserving much more attention. One early example is the reductive amination of

furfural with octan-1-amine promoted by Ni nanoparticles via the transfer hydrogenation strategy with using 2-propanol as reductant, where 30% yield of *N*-(furan-2-ylmethyl)octan-1-amine was obtained at 76 °C in 48 h [87].

3 Reductive amination of 5-hydroxymethylfurfural

Cellulosic biomass-derived 5-hydroxymethylfurfural (HMF) is a renewable platform molecule, which represents a starting material to obtain sustainable access to various bio-fuels and fine chemicals [88-90]. Analogously to furfural, reductive amination of HMF constitutes a significant fundamental route for the sustainable production of nitrogen-containing compounds from renewable biomass [91, 92]. Nowadays, studies on the reductive amination of HMF are primarily focused on adopting pressurized hydrogen or sodium borohydride as reductant.

3.1 Using gaseous hydrogen as reductant

3.1.1 Noble metal-based catalysts

As illustrated in Scheme 5a and similar to the reaction pathway of reductive amination of furfural, the reductive amination of HMF with aniline involves condensation of HMF with aniline to generate imine followed by hydrogenation to form amine. Zhang *et al.* tested various Ru-based complexes and found Ru(DMP)₂Cl₂, dichlorobis(2,9-dimethyl-1,10-phenanthroline)ruthenium(II), to be the best catalyst for the reductive amination of HMF with aniline providing 68% yield of *N*-phenyl-5-(hydroxymethyl)-2-furfuryl amine at 50 °C with 1.2 MPa H₂ after 5 h (entry 1, Table 4) [93]. The catalytic performance of Ru(DMP)₂Cl₂ was affected greatly by reaction temperature, as exemplified by the target product yield sharply increased to 98% when the reaction temperature was elevated to 60 °C (entry 2, Table 4) where after it remained unchanged at higher temperature (entry 3, Table 4). Several primary and secondary aromatic amines were used as nitrogen-source for the reductive amination of HMF to test the scope and limitations of the established catalytic system. Exhilaratingly, the reactions of aromatic amines proceeded

successfully resulting in good yields (65-90%) towards the corresponding target products with the exception of aromatic amines embracing large steric hindrance or bearing electron-withdrawing groups [93].

Currently, interest in the development of heterogeneous catalysts for the reductive amination of HMF is growing irrespectively of the excellent activity of the homogeneous Ru-complex catalyst. Pd supported on carbon or Al₂O₃ was found to be very effective for the reductive amination of HMF with aniline [94], leading to 100 or 95% yield of *N*-phenyl-5-(hydroxymethyl)-2-furfuryl amine under the conditions of 100 °C, 1 h and 0.3 MPa H₂ (entries 4 and 5, Table 4), respectively. Inferior activity of Pd/Al₂O₃ compared to Pd/C was attributed to the presence of Pd (111) crystal facets, which facilitated the hydrogenation of the furan ring as demonstrated by IR-CO measurements [94]. In addition, the authors found that the particle size of Pd showed no influence on the activity of the Pd/C catalyst. As expected, the heterogeneous Pd/C catalyst could easily be separated and maintained almost its original activity in three successive reuse tests.

Table 4 Reductive amination of HMF with aniline over noble metal-based catalysts

Entry	Catalyst	Nitrogen source	P _{H2} (MPa)	Temp. (°C)	Time (h)	Conv. (%)	Yield (%) ^a	Ref.
1	Ru(DMP) ₂ Cl ₂	Aniline	1.2	50	5	-	68	[93]
2	Ru(DMP) ₂ Cl ₂	Aniline	1.2	60	5	-	98	[93]
3	Ru(DMP) ₂ Cl ₂	Aniline	1.2	80	5	-	98	[93]
4	1% Pd/Al ₂ O ₃	Aniline	0.3	100	1	100	95	[94]
5	1% Pd/C	Aniline	0.3	100	1	100	100	[94]

^a The yield of *N*-phenyl-5-(hydroxymethyl)-2-furfuryl amine

In addition to monoamines, diamines can also be synthesized from the reductive amination of HMF. For example, 2,5-bis(aminomethyl)furan, a versatile feedstock for the production of polymer materials, was successfully produced from the reductive amination of HMF with ammonia in the presence of a Ru-complex catalyst as shown in Scheme 5b [95]. Approximate 65% yield of 2,5-bis(aminomethyl)furan was

obtained at 150 °C after 4 h with 0.25 MPa of H₂. Application of 2,5-bis(aminomethyl)furan as starting material for the manufacture of long-chain polyamides was also presented by the authors, highlighting the importance of reductive amination in the upgrading of HMF into polymers.

Bis(hydroxymethylfurfuryl)amine is another fundamental furan-based monomer applied for functional biopolymers, which smoothly can be synthesized from the reductive amination of HMF. Zhang *et al.* demonstrated in 2016 that the reductive amination of HMF with *n*-heptylamine resulting in 90.3% yield of bis(hydroxymethylfurfuryl)amine at 110 °C with 2 MPa of H₂ after 12 h employing Ru-complex catalyst (*i.e.*, Ru(DMP)₂Cl₂) as catalyst [96]. As displayed in Scheme 5c, the formation of bis(hydroxymethylfurfuryl)amine is a tandem reaction comprising condensation of HMF with *n*-heptylamine to give imine followed by hydrogenation to form the amine, which after subsequent addition reaction, dehydration and hydrogenation yield bis(hydroxymethylfurfuryl)amine. The authors claimed through comparison experiments and X-ray photoelectron spectroscopy analysis that the synergistic effect of Ru²⁺ and DMP ligand was accountable for the remarkable catalytic performance of the Ru-complex catalyst [96].

Scheme 5 (a) Reductive amination of HMF with aniline to yield *N*-phenyl-5-(hydroxymethyl)-2-furfuryl amine [93], (b) Reductive amination of HMF with ammonia to yield 2,5-bis(aminomethyl)furan [95], (c) Reductive amination of HMF with *n*-heptylamine to yield bis(hydroxymethylfurfuryl)amine [96]

3.1.2 Non-noble metal-based catalysts

Advantages associated with the employment of non-noble metal-based catalysts for organic reactions are well-known [97], and the development of non-noble metal-based catalysts for the reductive amination of HMF is progressing. Some representative non-noble metal-based catalysts are compiled in Table 5 [98-102]. Lin and co-workers performed the reductive amination of HMF in aqueous ammonia using Ni immobilized on SBA-15, and the results showed that the yield towards 5-aminomethyl-2-furylmethanol was significantly influenced by the loading of Ni [98] as the yield increased from 79.1% for Ni/SBA-15 (1.56 wt%) to 89.8% for Ni/SBA-15 (2.34 wt%) (entries 1 and 2, Table 5). Nevertheless, the activity of Ni/SBA-15 (2.34 wt%) gradually declined in five consecutive reaction runs, which resulted from coexistence of agglomeration, oxidation and loss of nickel species along

with carbon deposition as evident from XRD, H₂-TPR, SEM and TEM measurements of the used catalyst. Shi and co-workers reported a similar method for the reductive amination of HMF with ammonia using a series of Ni_yAlO_x catalysts with different Ni/Al molar ratio [99]. The highest yield of 5-aminomethyl-2-furylmethanol was here obtained with Ni₆AlO_x under the conditions of 100 °C, 6 h and 0.1 MPa H₂ (entry 3, Table 5). A control experiment using NiO_x catalyst provided an inferior yield of the targeted product under analogous reaction conditions, clearly uncovering a critical role of Al in the Ni_yAlO_x catalyst. A good substrate scope was confirmed with the Ni₆AlO_x catalyst for the reductive amination of HMF with various aromatic and aliphatic aldehydes and ketones, which resulting in over 80% yields of the corresponding targeted products. However, a significant loss in activity was observed for the catalyst because of partial re-crystallisation of the originally amorphous Al₂O₃ phase in the course of the reaction [99]. To develop a stable and durable heterogeneous catalyst for the reductive amination of HMF with NH₃, graphitic shell-encapsulated Co nanoparticles supported on carbon was fabricated by pyrolysis of Co-DABCO-TPA MOFs on carbon in which the MOF was prepared from cobalt nitrate, 1,4-diazabicyclo[2.2.2]octane (DABCO) and terephthalic acid (TPA) [100]. Co-DABCO-TPA@C-800 exhibited remarkable activity for the synthesis of 5-aminomethyl-2-furylmethanol (*i.e.*, 89% yield), and was found to be a stable and durable catalyst for the reductive amination of aldehydes, including HMF, due to encapsulation of the Co nanoparticles by the graphitic shell. 2,5-Bis(aminomethyl)furan, instead of 5-aminomethyl-2-furylmethanol, could also be produced by the reductive amination of HMF with NH₃ when Raney Ni or Raney Co was adopted as catalyst. The yield of 2,5-bis(aminomethyl)furan obtained with Raney Ni was superior to that with Raney Co as the latter preferentially promoting the formation of 5-aminomethyl-2-furylmethanol or other undesirable hydrogenation products (entries 6 and 7, Table 5). Unfortunately, Raney Ni suffered distinct activity loss during four recycles caused by the formation of Ni₃N on the surface of the Raney Ni during the repeating use as reported by Wei *et al.* [101].

Table 5 Reductive amination of HMF over non-noble metal-based catalysts

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DOI: 10.1039/D0GC01869D

Entry	Catalyst	Nitrogen source	P _{H2} (MPa)	Temp. (°C)	Time (h)	Conv (%)	Yield (%) ^a	Ref.
1	Ni/SBA-15 (1.56 wt%)	NH ₃ aqueous solution	1.5	100	4	-	79.1 ^b	[98]
2	Ni/SBA-15 (2.34 wt%)	NH ₃ aqueous solution	1.5	100	4	-	89.8 ^b	[98]
3	Ni ₆ AlO _x	NH ₃ (49 equiv.) ^a	0.1	100	6	100	99 ^b	[99]
4	NiO _x	NH ₃ (49 equiv.) ^a	0.1	100	6	91	33 ^b	[99]
5	Co-DABCO- TPA@C-800	NH ₃ (5-7 bar)	4.0	120	15	-	89 ^b	[100]
6	Raney Ni	NH ₃ (0.35 MPa)	1.0	160	12	100	60.7 ^c	[101]
7	Raney Co	NH ₃ (0.35 MPa)	1.0	160	12	100	14.8 ^c	[101]

^a Relative to molar of HMF.^b The yield of 5-aminomethyl-2-furylmethanol.^c The yield of 2,5-bis(aminomethyl)furan.

Recently, a novel strategy for the efficient synthesis of 2,5-bis(aminomethyl)furan from the reductive amination of HMF was developed by Lin and co-workers [102]. As described in Scheme 6, the synthesis from HMF included Ritter reaction and sequential reductive-amination as well as hydrolysis reaction. In the case of the Ritter reaction, the reaction of HMF with acetonitrile in methanol was successfully carried out by combined use of trifluoromethane sulfonic acid and P₂O₅, giving 67.2% yield of *N*-acyl-5-aminomethyl furfural at 100 °C. Subsequently, the isolated *N*-acyl-5-aminomethyl furfural acted as a starting material for the production of 2,5-bis(aminomethyl)furan through reductive amination promoted by Raney Ni under hydrogen atmosphere (1.5 MPa) followed by the hydrolysis catalyzed by hydrochloric acid, ultimately producing 60.8% yield of 2,5-bis(aminomethyl)furan. The starting point and significance of the established methodology is to prevent the generation of secondary amines, thus aiming towards selective synthesis of 2,5-bis(aminomethyl)furan.

Scheme 6 Synthesis of 2,5-bis(aminomethyl)furan from HMF via Ritter reaction, reductive amination and hydrolysis [102]

3.2 Other reductants

Apart from gaseous H_2 , cheap NaBH_4 is a prevalent reducing agent in organic synthesis, as already mentioned. The reductive amination of HMF with NaBH_4 as reductant was pioneered by Cukalovic and Stevens [103] adopting a two-step strategy without the need of a catalyst. Typically, HMF was reacted with aniline in water at room temperature for 5 h, where after the reaction was continued for 1 h after addition of NaBH_4 , eventually giving rise to 92% yield of 5-aminomethyl-2-furylmethanol [103], which could be separated from the reaction mixture by simple extraction using diethyl ether as extracting agent. Furthermore, the established system with NaBH_4 as reductant and two-step strategies in methanol or ethanol, rather than in water, also exhibited excellent performance for the reductive amination of HMF, clearly uncovering the good applicability of the system. Likewise, the employment of $\text{NaBH}(\text{OAc})_3$ as reductant was also developed for the reductive amination of HMF as reported by Ananikov *et al.* [104].

Recently, the combination of carbon monoxide and water has proven capable of serving as a good reducing agent for hydrogenation reactions in organic chemistry [105, 106]. The application of CO and H_2O as reductant for the reductive amination of

HMF with aniline was firstly performed by Cao and co-workers [107]. Here an efficient catalyst comprising Au nanoparticles supported on pure rutile TiO_2 demonstrated outstanding catalytic performance producing over 99% yield of 5-aminomethyl-2-furylmethanol in methanol/ H_2O (volume ratio 1/1) under the reaction conditions of 60 °C, 5 h and 2.0 MPa H_2 . Based on a series of control experiments, the authors proposed a plausible reaction mechanism shown in Scheme 7. Here, CO was initially adsorbed and activated by Au nanoparticles (step 1), the activated CO subsequently reacted with H_2O resulting in the formation of $\text{Au}^0\text{-H}$ species (step 2). Afterwards, the $\text{Au}^0\text{-H}$ species reduced the imine formed *in situ* from condensation of HMF with aniline giving the targeted product (steps 3 and 4). A broad range of aromatic primary and secondary amines containing electron-donating or -withdrawing functional groups was subjected to the established catalytic protocol as nitrogen source, and the reactions with HMF proceeded well providing good to excellent yields (60-99%) of the corresponding targeted products, unambiguously pointing out the robustness and effectiveness of the established methodology.

Scheme 7 Plausible reaction mechanism for the reductive amination of HMF using CO and H_2O as reductant [107]

3.3 Reactivity comparison of furfural and HMF in reductive amination

The reactivity of furfural and HMF in reductive amination with ammonia using gaseous hydrogen as reductant over non-noble metal-based catalysts is compared in detail in Figure 2. 65.1% and 98.9% yield of furfurylamine were obtained from the reductive amination of furfural with gaseous ammonia (0.1 MPa) over Raney Ni and Raney Co, respectively, under the conditions of 120 °C, 1.0 MPa H₂ and 2 h [54]. Nevertheless, 2,5-bis(aminomethyl)furan, instead of 5-aminomethyl-2-furylmethanol, was obtained as a dominant product when Raney Ni or Raney Co was used to catalyze the reductive amination of HMF with gaseous ammonia (0.35 MPa) [101]. This was a consequence of the formed 5-aminomethyl-2-furylmethanol being susceptible to further reductive amination in the presence of Raney Ni or Raney Co catalyst. In contrast, other reported Ni- or Co-based catalysts (*i.e.*, Ni₆AlO_x [99] and Co-DABCO-TPA@C-800 [100]) also exhibited remarkable performance for the reductive amination of HMF with gaseous ammonia to exclusively produce 5-aminomethyl-2-furylmethanol (yields of 99% and 89%) under mild conditions (T ≤ 120 °C). Thus, it seems that the reactivity of HMF in the reductive amination with gaseous ammonia is superior to furfural in terms of target product yield and reaction conditions.

In addition, the reductive amination of HMF in ammonia aqueous solution appeared to proceed more smoothly than that of furfural. For instance, higher yield (89.8%) of 5-aminomethyl-2-furylmethanol was obtained from the reductive amination of HMF in ammonia aqueous solution over Ni/SBA-15 under milder conditions (100 °C, 1.5 MPa H₂ and 4 h) [98], in comparison with only 73% yield of furfurylamine being obtained from reductive amination of furfural in ammonia aqueous solution over Fe₃O₄@SiO₂-Ni under the conditions of 115 °C (conventional heating), 2.0 MPa H₂ and 12 h [55]. Although the tested catalysts for reductive amination of furfural or HMF are different, the observed results could provide reference and evidence for the high reactivity of HMF in reductive amination. It is speculated that the superior reactivity of HMF in reductive amination is related to the electron-donating effect of

the hydroxymethyl group.

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DOI: 10.1039/D0GC01869D

		Product	Yield
Conversion: 100% Raney Ni, 0.1 MPa NH ₃ , 1.0 MPa H ₂ , 120 °C, 2 h Ref. 54		65.1%	
	Conversion: 100% Raney Co, 0.1 MPa NH ₃ , 1.0 MPa H ₂ , 120 °C, 2 h Ref. 54		98.9%	
	Conversion: 100% Fe ₃ O ₄ @SiO ₂ -Ni, NH ₃ aqueous solution (25 wt%), 2.0 MPa H ₂ , 115 °C (microwave-Assisted heating), 3 h Ref. 55		100%	
	Conversion: 100% Fe ₃ O ₄ @SiO ₂ -Ni, NH ₃ aqueous solution (25 wt%), 2.0 MPa H ₂ , 115 °C (conventional heating), 12 h Ref. 55		73%
Conversion: 100% Ni ₆ AlOx, NH ₃ (49 equiv.), 0.1 MPa H ₂ , 100 °C, 6 h Ref. 99		99%	
	Conversion: -- Co-DABCO-TPA@C-800, 0.6 MPa NH ₃ , 4 MPa H ₂ , 120 °C, 15 h Ref. 100		89%	
	Conversion: -- Ni/SBA-15, NH ₃ aqueous solution, 1.5 MPa H ₂ , 100 °C, 4 h Ref. 98		89.8%	
	Conversion: 100% Raney Ni, 0.35 MPa NH ₃ , 1.0 MPa H ₂ , 160 °C, 12 h Ref. 101		60.7%	
	Conversion: 100% Raney Co, 0.35 MPa NH ₃ , 1.0 MPa H ₂ , 160 °C, 12 h Ref. 101		14.8%	

Figure 2 Reductive amination of furfural or HMF with ammonia over non-noble metal-based catalysts using hydrogen gas as reductant

4 Reductive amination of levulinic acid

Levulinic acid (LA) is a versatile platform molecule derived from both cellulose and hemicellulose via multiple catalytic reactions, including sequential hydrolysis, dehydration and rehydration or hydrogenation/rehydration [108]. In particular, alkyl levulinates are also hailed as key bio-based platform molecules, since the chemical properties of alkyl levulinates are quite similar to LA and they also can be efficiently produced from cellulose or hemicelluloses [109]. Starting from LA or its esters, a wide range of useful chemicals such as, *e.g.* γ -valerolactone, 1,4-pentanediol, succinic acid, valerate esters, 2-methyltetrahydrofuran and

N-substituted-5-methyl-2-pyrrolidones could become accessible [110]. Especially, *N*-substituted-5-methyl-2-pyrrolidones, derived from the reductive amination of LA or its esters, are an important class of chemicals extensively applied in pharmaceuticals, surfactants, agrochemicals and dispersants and as commodity solvents in organic synthesis [111-113]. As depicted in Scheme 8, a three-step reaction pathway is proposed for the synthesis of *N*-substituted-5-methyl-2-pyrrolidones from the reductive amination of LA, encompassing the generation of an imine intermediate followed by hydrogenation and cyclisation. Moreover, a sequence of condensation-cyclisation-hydrogenation reactions has also been identified for the transformation of LA to *N*-substituted-5-methyl-2-pyrrolidone, but the former reaction pathway is prevailing in recent studies. Various strategies including using both gaseous H₂, formic acid and hydrosilane as reductant have been applied for sustainable synthesis of *N*-substituted-5-methyl-2-pyrrolidones from reductive amination of LA or its esters [113].

Scheme 8 Reaction pathway for the synthesis of *N*-substituted-5-methyl-2-pyrrolidones from the reductive amination of LA [111]

4.1 Using gaseous hydrogen as reductant

In general, gaseous H₂ is the most used reductant for the reductive amination of LA or its esters, and many metal-based (preferably noble metal) catalysts have been determined as effective catalysts for the LA-to-*N*-substituted-5-methyl-2-pyrrolidones

transformation with using H₂ as reductant.

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DOI: 10.1039/D0GC01869D

4.1.1 Noble metal-based catalysts

Fischmeister and co-workers [114] described a zwitterionic iridium complex catalyst with 2,2'-dipyridylamine ligand as effective for the synthesis of *N*-substituted-5-methyl-2-pyrrolidones from reductive amination of LA with 4-methoxyaniline under the conditions of 110 °C, 16 h and 0.5 MPa H₂. At full LA conversion a 100% selectivity towards product was achieved (entry 1, Table 6). The established catalytic system was applicable to various other linear and branched primary amines, bulky aromatic amines as well as hydrolysate derived from glucose, however, the homogeneous catalyst brought inconveniences in catalyst separation and reuse. In opposite, heterogeneous catalysts are attractive counterparts for practical production owing to their characteristic of easy separation. Exhilaratingly, the first Ir-based heterogeneous catalyst composed of metallic Ir supported on sulfonic acid functionalized SiO₂ was also excellent for the reductive amination of LA, providing 100% selectivity towards product as well (entry 2, Table 6) [115]. On the basis of DRIFT spectra of the catalyst at different reaction times and DFT calculations, the authors claimed that both metallic Ir and the sulfonic acid groups played a vital role in the reductive amination of LA with the sulfonic acid groups promoting the formation of imine and Ir facilitating the hydrogenation of the formed imine. A possible reaction mechanism was accordingly proposed by the authors for the reductive amination of LA with aniline in the presence of Ir/SiO₂-SO₃H (Scheme 9). The tandem reaction involved interacting of the sulfonic acid groups with the carboxylic group of LA to quickly promote the formation of imine intermediate (step 1 and 2) followed by hydrogenation of imine facilitated by Ir nanoparticles (step 3) to give amine intermediate and subsequently cyclisation to yield *N*-substituted-5-methyl-2-pyrrolidone (step 4). Analogously, a prominent role of acid sites in promoting the reductive amination of LA was also discovered by Xiao *et al.* through screening different metal oxides (*e.g.*, Al₂O₃, TiO₂ and ZrO₂) as carriers to support Pd nanoparticles [116]. The optimal carrier was observed to be ZrO₂ comprising abundant strong Lewis acid sites, which could increase the electrophilicity

of the carbonyl group in LA. This greatly facilitated the amination of LA to generate the imine intermediate and thereby prevented the undesirable hydrogenation reaction (e.g., hydrogenation of LA to γ -valerolactone).

Scheme 9 The possible reaction mechanism for the reductive amination of LA with aniline over Ir/SiO₂-SO₃H catalyst [115]

In another attempt reported by Iborra *et al.*, metallic Pt loaded on TiO₂ was capable of smoothly catalyzing the reductive amination of ethyl levulinate with aniline with a high 93% yield of target product (entry 4, Table 6) [117]. In addition, the established protocol was determined to tolerate a wide range of amines. Subsequently, the noteworthy work of Iborra *et al.* on developing Pt/TiO₂ as an effective catalyst for the reductive amination of LA has impelled the development of more durable Pt-based catalysts (*i.e.*, Pt-MoO_x/TiO₂ [118], Pt/TiO₂-NTs [119] and Pt/P-TiO₂ [120]) for the reductive amination of LA or its esters (entries 5-7, Table 6). The remarkable catalytic behavior of Pt-MoO_x/TiO₂ under mild conditions (100 °C, 0.3 MPa H₂) was

elucidated to be related to the presence of Mo_x with high acidity [118]. For Pt/ TiO_2 -NTs (TiO_2 nanotubes) catalyst, direct one-pot cascade synthesis of *N*-substituted-5-methyl-2-pyrrolidones from reductive amination of ethyl levulinate with nitrobenzene proceeded well, in which the *in situ* formed aniline from nitrobenzene hydrogenation acted as nitrogen sources [119]. Combining control experiments and catalyst characterisation the lower acidity of TiO_2 -NTs was presumed to be responsible for the superior performance of the Pt/ TiO_2 -NTs relative to Pt/ TiO_2 , since the higher acid strength of the latter resulted in strong adsorption of nitrobenzene. In the case of Pt/P- TiO_2 (Pt nanoparticles immobilized on porous TiO_2 nanosheets) [120], unprecedented catalytic performance was obtained for the reductive amination of LA with *n*-octylamine. Up to 97% yield of *N*-substituted-5-methyl-2-pyrrolidones was achieved at room temperature in only 1 h with 0.1 MPa of H_2 (entry 7, Table 6). Nitrogen adsorption-desorption and *in situ* acetone-DRIFT together with *in situ* CO-DRIFT measurements of the Pt/P- TiO_2 catalyst demonstrated, that the strong acidity of the TiO_2 carrier along with the low electron density of the metallic Pt sites and the porous structure of the TiO_2 nanosheets accounted for the outstanding performance. Moreover, the Pt/P- TiO_2 catalyst featured excellent activity for the reductive amination LA or its esters with a broad variety of amines at ambient temperature and H_2 pressure [120]. Apart from metallic Ir-, Pd- and Pt-based catalysts, a Ru-based catalyst has also exhibited high activity for the production of *N*-substituted-5-methyl-2-pyrrolidones from reductive amination of ethyl levulinate [121].

Previously reports on the reductive amination of LA, or its esters, have concentrated on batch reactions. Continuous flow reactions offer industrial advantages in large-scale application compared to batch reactions, *e.g.*, energy efficiency, improved thermal management and waste reduction [122,123]. Pioneering work in using a continuous flow strategy for the reductive amination of LA was performed by Luque and co-workers [122]. The authors reported that Ru supported on TiO_2 enabled the reaction to proceed well in a flow reactor, affording 67.2% yield of

N-substituted-5-methyl-2-pyrrolidones with 79% conversion of LA at 90 °C (entry 9, Table 6). Notably, the preparation of TiO₂ adopted a mechanochemical method using orange peel residues as sacrificial template, highlighting the sustainability of the synthetic procedure. Recently, *g*-C₃N₄/Pt (i.e., graphitic carbon nitride functionalized with platinum loading) was reported by the same authors, which resulted in acceptable activity in a continuous flow reactor (entry 10, Table 6) [123]. Additionally, a recent work reported by Sun *et al.* demonstrated that C-Au₆₆Pd₃₄ (AuPd alloy nanoparticles with a Pd content of 34 mol%) was highly active for the reductive amination of ethyl levulinate with *n*-octylamine (entry 11, Table 6) [124].

Table 6 The synthesis of pyrrolidones from reductive amination of levulinic acid or its esters with amines using gaseous H₂ as reductant

Entry	Catalyst	Nitrogen source	P _{H2} (MPa)	Temp. (°C)	Time (h)	Conv. (%)	Yield (%) ^a	Ref.
1	Zwitterionic iridium complex	4-Methoxyaniline	0.5	110	16	98	98	[114]
2	Ir/SiO ₂ -SO ₃ H	Aniline	3.4	100	8	63	63	[115]
3	Pd/ZrO ₂	<i>n</i> -Octylamine	0.5	90	12	100	98.7	[116]
4 ^b	Pt/TiO ₂	Aniline	1.0	120	6	98	93	[117]
5	Pt-MoO _x /TiO ₂	<i>n</i> -Octylamine	0.3	100	20	100	99	[118]
6 ^b	Pt/TiO ₂ -NTs	Nitrobenzene	1.0	120	48	94	92	[119]
7	Pt/P-TiO ₂	<i>n</i> -Octylamine	0.1	r.t.	1	-	97	[120]
8 ^b	Ru-PP/CNT	<i>n</i> -propylamine	3.0	120	24	99.4	98.7	[121]
9 ^c	Ru/TiO ₂	Acetonitrile	5	90	-	79	67.2	[122]
10 ^c	<i>g</i> -C ₃ N ₄ /Pt	Acetonitrile	5	90	-	37	25	[123]
11 ^b	C-Au ₆₆ Pd ₃₄	<i>n</i> -Octylamine	0.1	85	12	-	99	[124]
12 ^d	Pd/C	Aspartic acid	5	70	24	-	95	[125]
13	CNF ₃₀ @Ni@CNTs	Benzyl amine	3.0	130	6	100	99	[126]
14	Cu ₁₅ Pr ₃ /Al ₂ O ₃	<i>n</i> -Octylamine	5.0	175	20	-	92	[127]

^a Yield of *N*-substituted-5-methyl-2-pyrrolidones.

^b The substrate was ethyl levulinate.

^c Performed in a continuous flow reactor.

^d The substrate was methyl levulinate.

Very recently, a green strategy using biomass-derived amine as nitrogen source for the reductive amination of methyl levulinate was developed by Zinck and co-workers [125]. In their work, aspartic acid - an amino acid existing in plants or accessible from

bio-based sugars - served as a promising nitrogen source in the reductive amination of methyl levulinate obtaining 95% yield of the corresponding *N*-substituted-5-methyl-2-pyrrolidone in the presence of Pd/C catalyst under mild conditions (70 °C, 24 h and 5 MPa of H₂) (entry 12, Table 6). This work highlights new possibilities in the sustainable synthesis of *N*-substituted-5-methyl-2-pyrrolidones from renewable biomass, and renders the synthetic procedure to become greener and more attractive.

4.1.2 Non-noble metal-based catalysts

Despite the significant progress made with noble-metal catalysts, the development of none-noble metal-based catalysts for the reductive amination of LA or its esters is a desired goal of the technology. An innovative catalyst comprising Ni nanoparticles stabilized by coating porous-carbon and loaded on carbon nanotubes, namely CNF₃₀@Ni@CNTs, was developed for the reductive amination of LA and benzyl amine [126]. The CNF₃₀@Ni@CNTs catalyst yielded excellent results (100% conversion, 99% yield) under reaction conditions of 130 °C, 6 h and 3.0 MPa H₂, and exhibited also recyclability of up to twenty times without any appreciable loss of activity. As evidenced from catalyst characterisation, the extraordinary stability of CNF₃₀@Ni@CNTs was attributed to the protection with porous carbon, which could effectively prevent the Ni nanoparticles against leaching and sintering in the course of the reaction. Furthermore, a distinct, but convincing, reaction pathway different from previously reported reaction pathways was proposed for the reductive amination of LA with benzyl amine by the authors from NMR and IR spectroscopy as well as high-resolution mass spectrometry measurements combined with verification experiments and DFT calculations [126]. Here, as presented in Scheme 10, an amide intermediate (**M1**) formed initially followed by cyclisation of **M1** into **M2** intermediate which subsequently dehydrated into the **M3** intermediate, which finally underwent hydrogenation forming the desirable *N*-substituted-5-methyl-2-pyrrolidone (*i.e.*, 1-benzyl-5-methylpyrrolidin-2-one) product. Other non-noble metal-based catalyst such as Cu₁₅Pr₃/Al₂O₃ [127] was also exploited for the reductive amination of

LA with *n*-octylamine, and resulted in remarkable results but under relatively harsh conditions (175 °C) (entry 14, Table 6).

Scheme 10 Plausible reaction pathway for the reductive amination of LA with benzyl amine over CNF₃₀@Ni@CNTs [126]

4.2 Using formic acid as reductant

Since formic acid is formed in equal amounts as LA during acid catalyzed dehydration of carbohydrates and it has been verified as a promising liquid hydrogen source, many efforts have been devoted to using formic acid as reductant for the reductive amination of LA and some representative examples are summarized in Table 7 [128-136]. Homogeneous Ru- or Ir-based complex catalysts have been employed with success in the reductive amination of LA and resulted in good to excellent yields of targeted *N*-substituted-5-methyl-2-pyrrolidones (entries 1-3, Table 7) [128-130]. The established catalytic protocol based on these complex catalysts also worked well for a broad variety of amines including aliphatic and aromatic amines. More importantly, the catalytic systems were also successfully applicable to an aqueous mixture containing LA and formic acid derived from acidic dehydration of glucose with two-step tandem processes as illustrated in Scheme 11. Ultimately, acceptable yields of target products (23-35%) were directly attained from glucose, emphasizing the broad applicability of the catalytic system [128, 130].

Scheme 11 One-pot synthesis of *N*-substituted-5-methyl-2-pyrrolidones from glucose [128, 130]

The effective homogeneous catalytic systems are, however, less prone for large-scale industrial application owing to the expensive noble-metal complex catalysts and their difficult separation and recycling. Hence, significant attention has been directed instead to development of effective heterogeneous catalysts. For example, Au/ZrO₂ prepared by a modified deposition precipitation procedure [131] could function as an effective catalyst for the reductive amination of LA with benzylamine, producing 97% yield of the corresponding pyrrolidone at 130 °C in 12 h (entry 4, Table 7). Likewise, a series of NHC-based coordination polymer catalysts were prepared from *p*-phenylene-bridged bis-benzimidazolium salts and metal precursors through a self-assembly process, and subsequently used for the reductive amination of LA with ammonium formate [132]. Interestingly, inexpensive ammonium formate acted as both nitrogen and hydrogen sources in this work leading to 5-methyl-2-pyrrolidone as a target product, accompanied by CO₂ release. Among the examined catalysts, a NHC-Ru coordination polymer was found to be best for the synthesis of 5-methyl-2-pyrrolidone, furnishing a high 91% yield under mild conditions (120 °C and 24 h) (entry 5, Table 7). Furthermore, the NHC-Ru coordination polymer catalyst demonstrated to maintain its original activity in 37 consecutive reaction runs [132]. Intriguingly, the synthesis of *N*-substituted 5-methyl-2-pyrrolidones, instead of 5-methyl-2-pyrrolidone, was realized with similar good results by one-pot, tandem reductive amination of LA, ketones/aldehydes and ammonium formate.

The good performance of the noble metal-based catalysts in the reductive amination of LA using formic acid as reductant can also be obtained with non-noble

metal-catalysts such as $\text{Fe}_3(\text{CO})_{12}$ [133] and Raney-Ni [134] under more harsh reaction conditions (*i.e.*, 180 °C) (entries 6-7, Table 7). The versatility of $\text{Fe}_3(\text{CO})_{12}$ as catalyst was unambiguously demonstrated with an extensive substrate scope and by smoothly facilitating the reductive amination of crude LA solutions originating from acid hydrolysis of sugarcane bagasse [133].

Interestingly, an innovative synthesis strategy without catalyst was developed by Xiao *et al.* for the reductive amination of LA with benzylamine in dimethylsulfoxide (DMSO) providing to up to 87% yield of *N*-substituted-5-methyl-2-pyrrolidone under mild conditions (entry 8, Table 7) [135]. The authors found that the DMSO played a significant, but unclear role in the reductive amination of LA as low product yield was observed in other solvents. In addition, similar results were also obtained for the synthesis of other *N*-substituted 5-methyl-2-pyrrolidones with alternative amines instead of benzylamine, clearly demonstrating the general applicability of the described catalytic system [135]. The use of DCOOH as replace of HCOOH in the reductive amination further allowed exploring the corresponding reaction mechanism, where the formation of iminium intermediates from ^1H NMR suggested that the reaction proceeded analogously to the previously reported mechanism [135]. Zhang and co-workers pioneered the reductive amination of LA using formic acid in a continuous-flow microreactor, where the corresponding target *N*-substituted 5-methyl-2-pyrrolidone reached up to 78.8% at 150 °C (entry 9, Table 7) [136]. The observed results clearly demonstrated that the use of formic acid as reductant for reductive amination was also suitable for continuous production beside batch operation.

Table 7 The synthesis of pyrrolidones from reductive amination of levulinic acid with amines using formic acid as reductant

Entry	Catalyst	Nitrogen source	Temp. (°C)	Time (h)	Conv (%)	Yield (%) ^a	Ref.
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂ / <i>t</i> -Bu ₃ PH BF ₄	Benzylamine	120	12	-	95	[128]
2 ^a		Benzylamine	80	4	-	86	[129]
3		Aniline	60	17	-	97	[130]
4	Au/ZrO ₂ -VS	Benzylamine	130	12	98	97	[131]
5 ^b		NCOONH ₄	120	24	-	91	[132]
6	Fe ₃ (CO) ₁₂	Ethylamine	180	15	-	85	[133]
7 ^b	Raney-Ni	NCOONH ₄	180	3	100	94	[134]
8 ^c	No catalyst	Benzylamine	100	12	-	87	[135]
9 ^d	No catalyst	<i>n</i> -Butylamine	150	-	87.1	78.8	[136]

^a Aqueous HCOOH-HCOONa solution (pH = 3.5).

^b HCOONH₄ as both nitrogen source and hydrogen source.

^c Addition of triethylamine.

^d The reaction was conducted in a continuous-flow microreactor.

4.3 Using hydrosilane as reductant

Analogous to gaseous H₂ and formic acid, hydrosilane can also function as an effective reductive agent for the reductive amination of LA. For instance, Liu and co-workers demonstrated that the reductive amination of LA and aniline using triethoxysilane as reductant in the lactate-based ionic liquid 1-butyl-3-methylimidazolium lactate ([BMIm][Lac]), was very effective furnishing a high 95% yield of desirable *N*-phenyl-5-methyl-2-pyrrolidone at 80 °C after only 1 h of reaction (entry 1, Table 8) [137]. In addition, the [BMIm][Lac] system showed also high activity towards various substituted aromatic amines. The remarkable performance of the [BMIm][Lac] system was mainly associated with [BMIm][Lac]

entailing multiple roles, including the activation of hydrosilane and concurrently the catalytic promotion of the reductive amination of LA with amines. This deemed the authors to believe that the system holds great potential for large-scale application due to its outstanding activity together with the sustainability of the synthetic raw material (*i.e.*, lactic acid originated from biomass) [138]. The proposed reaction pathway for the reductive amination of LA using hydrosilane as reductant was by NMR analysis and control experiments found to involve interaction of [BMIm][Lac] with (EtO)₃SiH, and bore distinct resemblance to the reaction pathway reported for H₂ or formic acid as reductant. Thus, the possible reaction pathway was determined to follow a condensation-hydrogenation-cyclisation sequence with a sequence of condensation-cyclisation-hydrogenation existing in parallel, as depicted in Scheme 12. Another advantage related to the usage of hydrosilane was that the target product formation could be controlled allowing both *N*-substituted 5-methyl-2-pyrrolidones and *N*-substituted pyrrolidines to be exclusively obtained as shown in Scheme 12. Similar to *N*-substituted 5-methyl-2-pyrrolidones, *N*-substituted pyrrolidines are ubiquitous motifs in numerous biologically active compounds (*e.g.*, natural alkaloids) and pivotal versatile feedstocks in the pharmaceutical and agrochemical industries [139].

Scheme 12 Plausible reaction mechanism for the synthesis of *N*-substituted 5-methyl-2-pyrrolidones or *N*-substituted pyrrolidines from the reductive amination of LA using hydrosilane as reductant [141]

As reported above, significant efforts have concentrated upon the synthesis of *N*-substituted methyl-2-pyrrolidones with gaseous H₂ or formic acid employed as reducing agent by the reductive amination of LA, while the production of *N*-substituted pyrrolidines have been hardly addressed. In contrast, emphasis has been on the switchable synthesis of pyrrolidines vs pyrrolidinones with hydrosilane as reductant in the reductive amination of LA [140-143]. An early example of such switchable synthesis was described by Fu and co-workers using B(C₆F₅)₃ as catalyst [140]. Here, large amount of polymethylhydrosiloxane (5 equivalent) was favorable for the formation of *N*-substituted pyrrolidine while low amount of polymethylhydrosiloxane (2.5 equivalent) was conducive to the generation of *N*-substituted 5-methyl-2-pyrrolidone (entries 2 and 3, Table 8). Sakai and co-workers [141] studied the reductive amination of LA using phenylsilane as reductant, and showed that the selectivity towards *N*-substituted 5-methyl-2-pyrrolidone or *N*-substituted pyrrolidine could be tailored depending on the usage of catalyst and the loading amount of phenylsilane. For example, as high as 94% yield of *N*-substituted 5-methyl-2-pyrrolidone was achieved over In(OAc)₃ catalyst with one equivalent of phenylsilane at 120 °C, whereas *N*-substituted pyrrolidine was attained in a high yield of 92% in the presence of InI₃ and three equivalent of phenylsilane (entries 4 and 5, Table 8). Analogously, Liu *et al.* [142] presented that switching the catalyst from AlCl₃·6H₂O to RuCl₃·3H₂O resulted in selectivity to *N*-substituted 5-methyl-2-pyrrolidone instead of *N*-substituted pyrrolidine under mild conditions (entries 6 and 7, Table 8). Moreover, the established protocol could be elaborated to numerous *N*-substituted 5-methyl-2-pyrrolidones or *N*-substituted pyrrolidines using various amines as nitrogen source. Very recently, two *N*-heterocyclic carbene-based iron complexes (as indicated in Table 8) have also been employed in the reductive amination of LA using phenylsilane as reductant, successfully giving rise to *N*-substituted 5-methyl-2-pyrrolidone or *N*-substituted pyrrolidine in a high yields of 87 or 91%, respectively (entries 8 and 9, Table 8) [143].

Table 8 Reductive amination of levulinic acid with using hydrosilane as reductantView Article Online
DOI: 10.1039/D0GC01869D

Entry	Catalyst	Nitrogen source	Hydrosilane ^a	Temp. (°C)	Time (h)	Conv. (%)	Yield (%)	Ref.
1	[BMIm][Lac] ^b	Aniline	Triethoxysilane (2 equiv.)	80	1	-	95	[137]
2	B(C ₆ F ₅) ₃	Aniline	polymethylhydrosiloxane (2.5 equiv.)	100	13	-	91 ^c	[140]
3	B(C ₆ F ₅) ₃	Aniline	polymethylhydrosiloxane (5 equiv.)	100	13	-	86 ^d	[140]
4	In(OAc) ₃	Aniline	Phenylsilane (1 equiv.)	120	3	-	94 ^c	[141]
5	InI ₃	Aniline	Phenylsilane (3 equiv.)	120	24	-	92 ^d	[141]
6	AlCl ₃ ·6H ₂ O	Aniline	Phenylsilane (3 equiv.)	30	12	-	93 ^c	[142]
7	RuCl ₃ ·3H ₂ O	Aniline	Phenylsilane (4 equiv.)	45	24	-	93 ^d	[142]
8		Aniline	Phenylsilane (2 equiv.)	100 ^e	20	-	87 ^c	[143]
9		Aniline	Phenylsilane (6 equiv.)	100 ^e	20	-	91 ^d	[143]

^a The data in parenthesis refers to molar equivalent relative to LA.^b 1-butyl-3-methylimidazolium lactate.^c The target product was *N*-substituted-5-methyl-2-pyrrolidones.^d The target product was *N*-substituted pyrrolidines.^e Visible light irradiation.

5 Reductive amination of lignin model monomers

Lignin is an irregular and complex phenolic polymer comprising three phenyl propane units (*i.e.*, syringyl, guaiacyl, and *p*-hydroxyphenyl alcohol), thus constituting the most recalcitrant and complex constituent of lignocelluloses [144]. The development of efficient utilisation of lignin is slow-moving, relative to cellulose and hemicelluloses, due to its recalcitrant and complex structure [145, 146]. Nevertheless, significant advances have also been achieved in lignin valorisation over the past decade thanks to much investment in research [147, 148]. The most frequently used and effective strategy for lignin valorisation is lignin depolymerisation, which generated various phenolic model monomers (*e.g.*, phenol and substituted phenol)

[149]. Catalytic upgrading of lignin-derived phenolic model monomers into fine chemicals, polymer and fuels is current research hotspot [150]. Particularly, the reductive amination of lignin-derived phenolic model monomers represents one of the key processes in transforming lignin into useful chemicals.

Li *et al.* [151] have described a commercial Pd/C catalyst capable of facilitating the reductive amination of phenol with hydrazine or hydroxylamine to yield *N*-cyclohexyl aniline. Detailed investigations of the established catalytic system allowed substrate scope expansion to be done with results firmly demonstrated that the established catalytic system enabled various phenolic lignin model monomers to become important nitrogen-containing compounds, thus pointing out new possibilities in the synthesis of nitrogen-containing compounds from lignin derivatives. Another attempt to replace the highly corrosive hydrazine with organic amines for the reductive amination of phenol was pioneered by the same authors [152]. Interestingly, commercial Pd/C catalyst also featured the remarkable catalytic activity in the reductive amination of phenol with aniline using sodium formate as reductant, affording 95% yield of *N*-cyclohexyl aniline at 100 °C in 24 h (Scheme 13). Strikingly, the created protocol based on commercial Pd/C catalyst was discovered to tolerate an extensive substrate scope including a wide range of aniline derivatives or a broad variety of substituted phenols [152].

Scheme 13 Synthesis of nitrogen-containing compounds from the reductive amination of lignin-based phenolic model monomers [152-154]

Successively, the authors proposed a tentative reaction mechanism as delineated in Scheme 14 for the reductive amination of phenol with aniline [152]. The reaction initiated with the reduction of phenol into cyclohexanone in the presence of [Pd]/[H] followed by condensation of cyclohexanone with aniline to afford imine intermediate and subsequent hydrogenation of the imine intermediate into *N*-cyclohexyl aniline with the re-release of the active [Pd] sites.

Scheme 14 Tentative reaction mechanism for the reductive amination of phenol with aniline over Pd/C catalyst [152]

Fu and co-workers claimed that palladium hydride (PdH_x) supported on Al_2O_3 also exhibited prominent catalytic performance in the reductive amination of phenol with *p*-toluidine under H_2 atmosphere (1 atm) [153]. *N*-cyclohexyl-*p*-toluidine yield exceeding 94% along with 95% phenol conversion was obtained at 50 °C in 3 h. The prominent activity of $\text{PdH}_x/\text{Al}_2\text{O}_3$ under the mild conditions (*i.e.*, 50 °C) was considered to be associated to the high reactivity of PdH_x . Concomitantly, a positive effect in the activation of phenol played by Al_2O_3 was observed, which partly contributed to the excellent catalytic behavior [153]. In addition, extensive phenol derivatives and aniline derivatives were also applicable in this reaction and yielded

the corresponding *N*-substituted aniline analogues in moderate to good yields [153].

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DOI: 10.1039/D0GC01869D

Apart from aromatic amines, aliphatic amines as nitrogen source for the reductive amination of lignin-derived phenolic model monomers also allowed the reaction to proceed well. For example, the reductive amination of phenol with butylamine occurred smoothly over commercial Pd/C catalyst using sodium formate as reductant as illustrated in Scheme 13, resulting in full conversion of phenol with 96% yield of *N*-butyl-cyclohexylamine under the conditions of 60 °C and 6 h [154]. Importantly, the established catalytic system was further successfully applied in a continuous-flow reactor for the synthesis of cyclohexylamines in gram scale, showing great potential for actual industrial production.

Similar to *N*-cyclohexyl aniline, diphenylamine was accessible from the reductive amination of lignin-derived phenolic model monomers as delineated in Scheme 13. The first and unique example for the synthesis of diphenylamine from reductive amination of phenol was done by Li *et al.* [155] using Pd/C and ammonium formate as catalyst and nitrogen/hydrogen sources, respectively. Up to 98% yield of diphenylamine was achieved under argon atmosphere at 160 °C in 24 h. Moreover, the authors reported 17 different diarylamines synthesized from the reductive amination of phenols with moderate to excellent yields (25-98%) using the described catalytic system [155]. Furthermore, the authors clearly elaborated the possible reaction mechanism taking the reductive amination of phenol with ammonium formate as an example [155]. As exhibited in Scheme 15, Pd^{II} dihydride species (HPd^{II}H) and NH₃ were *in situ* generated from the decomposition of ammonium formate over Pd⁰ species accompanied with the release of CO₂. Next, the interaction of HPd^{II}H species and phenol led to the formation of cyclohexenone followed by condensation with NH₃ to give the imine. Afterwards, the resultant imine successively underwent condensation with cyclohexenone followed by two dehydrogenations in the presence of Pd⁰ species to yield the diphenylamine product.

Very recently, an innovative approach towards synthesis of 3,4-dialkoxyaniline from

lignin-derived 4-propylguaiacol with multiple steps was exploited by Maes and co-workers [156]. As described in Scheme 16, 4-propylguaiacol underwent etherification, oxidation, Beckmann rearrangement and alcoholysis in sequence to give rise to 3,4-dialkoxyaniline. Eventually, the yield of 3,4-dialkoxyaniline reached up to 65% in the multiple conversion processes, and this work is believed to provide new insights for the sustainable synthesis of nitrogen-containing compounds from lignin derivatives.

Scheme 15 Proposed reaction mechanism for the synthesis of diphenylamine from reductive amination of phenol over Pd/C catalyst [155]

Scheme 16 Reaction pathway for the synthesis of 3,4-dialkoxyaniline from lignin-derived 4-propylguaiacol [156]

6 Reductive amination of other biomass-derived compounds

Besides furfural, HMF, levulinic acid and lignin model monomers many other biomass-derived molecules have also been subjected to the upgrading strategy of reductive amination with an aim of attaining a diverse range of nitrogen-containing compounds. Some representative examples are summarized in this section.

6.1 Reductive amination of other furan derivatives

2,5-Diformylfuran (DFF), an oxidative derivative of HMF, is an attractive biomass-based molecule with various potential applications in polymers, pharmaceuticals and agrochemicals [157, 158]. Reductive amination of DFF has recently received increased attention as it allows access to symmetric binary amines, which are common units in polymers (*e.g.*, polyamides and polyurethanes) and resins [159-161]. Raney Ni, acid treated Raney Ni (AT-Raney-Ni) and hydrogen peroxide treated AT-Raney-Ni (H₂O₂-AT-Raney-Ni) were reported for catalyzing the reductive amination of DFF with ammonia using H₂ as reductant (Scheme 17a), in which AT-Raney-Ni exhibited the best catalytic performance offering 42.6% yield of 2,5-bis(aminomethyl)furan at 120 °C with 1.0 MPa of H₂ in 6 h [159]. After characterization of the as-prepared three catalysts, the authors found that higher content of Ni⁰ species together with larger surface area of AT-Raney-Ni was accountable for its superior behavior. Also, the authors reported that a moderate yield (42.6%) of 2,5-bis(aminomethyl)furan was ascribed to its high reactivity which induced further reaction with DFF to form polyamines [159]. Afterwards, Hoffmann and co-workers [160] employed a series of aliphatic amines instead of ammonia as nitrogen source for reductive amination of DFF in the presence of Raney Ni and NaBH₄ (Scheme 17b). The obtained nitrogen-containing tetrahydrofuran derivatives could be upgraded further into amphoteric surfactants with moderated yields (39-55%) [160]. Moreover, the as-fabricated amphoteric surfactants successfully went through tests of wetting properties and bactericidal activities with good results. Especially, the as-fabricated amphoteric surfactants were for the first time to be determined to be

efficient antifungal activity against *Fusarium graminearum* [160].

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Scheme 17 (a) Reductive amination of 2,5-diformylfuran into 2,5-bis(aminomethyl)furan [159], (b) synthesis of amphoteric surfactants from reductive amination of 2,5-diformylfuran [160], and (c) synthesis of 2,5-bis(aminomethyl)furan from 2,5-diformylfuran via 2,5-diformylfuran dioxime intermediate [161]

In order to solve the problem of low 2,5-bis(aminomethyl)furan yield caused by its high reactivity, a novel protocol comprising conversion of DFF into 2,5-diformylfuran dioxime and successive hydrogenation of 2,5-diformylfuran dioxime into 2,5-bis(aminomethyl)furan was firstly developed by Xu and co-workers [161]. As presented in Scheme 17c, DFF reacted with hydroxylamine at 110 °C for 2 h to give 2,5-diformylfuran dioxime and subsequently underwent hydrogenation over Rh/HZSM-5 under the conditions of 130 °C, 2.0 MPa of H_2 and 2 h to furnish

2,5-bis(aminomethyl)furan. Ultimately, the yield of 2,5-bis(aminomethyl)furan could reach to 80.3% in the two-step processes [161].

As a reductive derivative of HMF, 2,5-dihydroxymethylfuran is an interesting biomass-based molecule with promising application in the manufacture of functional polymers, synthetic resins and artificial fibers [162, 163]. Direct synthesis of nitrogen-containing compounds from reductive amination of 2,5-dihydroxymethylfuran can also take place successfully, and the integrated reaction process involves the dehydrogenation of 2,5-dihydroxymethylfuran into DFF followed by complying with the reaction pathway of reductive amination of DFF (Scheme 18a). As reported by Wang *et al.* [164], $\text{Cu}_{3/17}\text{Ni}_{6/17}\text{Al}_{8/17}\text{O}$ catalyst exhibited the highest catalytic performance among a series of $\text{Cu}_x\text{Ni}_y\text{Al}_z\text{O}$ catalysts with different Cu/Ni ratios in the reductive amination of 2,5-dihydroxymethylfuran with aniline. The reaction afforded over 99% conversion with 55% yield of *N,N'*-(furan-2,5-diylbis(methylene))dianiline under the conditions of 120 °C and 24 h without any external hydrogen sources. The results of catalyst characterisation demonstrated the presence of a Cu-Ni alloy phase was responsible for the superior activity of $\text{Cu}_{3/17}\text{Ni}_{6/17}\text{Al}_{8/17}\text{O}$ catalyst [164]. In addition, another advantage of the established catalytic system was that the *in situ* released H_2 from the dehydrogenation of 2,5-dihydroxymethylfuran supplied the H-donation required for hydrogenation of the imine intermediate to yield the target product.

Scheme 18 (a) Reductive amination of 2,5-dihydroxymethylfuran with aniline [164], (b) reductive amination of furfuryl alcohol with ammonia into furfurylamine or tetrahydrofurfurylamine [165]

Analogously to 2,5-dihydroxymethylfuran, furfuryl alcohol can also be upgraded into nitrogen-containing compounds through reductive amination as depicted in Scheme 18b. As reported by Li and co-workers [165], furfurylamine and tetrahydrofurfurylamine could be switchably synthesized over Raney Ni catalyst from the reductive amination of furfuryl alcohol with ammonia relying on whether 1.0 MPa H₂ was charged or not. Specifically, up to 94.0% yield of tetrahydrofurfurylamine was achieved in the presence of 1.0 MP H₂, while 78.8% yield of furfurylamine was attained without adding H₂ under the conditions of 180 °C and 48 h, respectively. The reaction pathway for the synthesis of furfurylamine from furfuryl alcohol included the dehydrogenation of furfuryl alcohol and subsequently furfural reductive amination (Scheme 18b). In parallel, the reaction pathway of tetrahydrofurfurylamine synthesis was similar with that of furfurylamine synthesis with the exception of involving the hydrogenation of the furan ring (Scheme 18b). Presently, reductive amination of many other biomass-derived alcohols are reported [166], thus anticipating to broaden the routes towards the synthesis of nitrogen-containing compounds from biomass.

5-Methylfurfural is accessible from biomass-derived carbohydrates and has similar chemical properties as furfural, and hailed as a perspective platform molecule owing to its reduced oxygen content and chemical stability [167,168]. Direct reductive amination of 5-methylfurfural with aniline has also been described by Yang and co-workers [169]. They found that Pd loaded on activated carbon exhibited high activity for this reaction offering 99% conversion of 5-methylfurfural and 99% yield of *N*-(5-methylfurfuryl)aniline at 50 °C with 0.4 MPa H₂ in 45 min (Scheme 19a). Moreover, when subjected to the established catalytic protocol a wide range of aniline derivatives bearing different substituent group on the benzene ring also afforded the corresponding target products in excellent yields (86-100%). Additional reports about reductive amination of other furan derivatives have also frequently emerged in recent years. For instance, a carbonyl-conjugated vinylfuran, derived from aldol condensation of furfural with methyl isobutyl ketone (as shown in Scheme 19b), was firstly reported by Vigier *et al.* [170] to undergo reductive amination to give nitrogen-containing compounds. They performed the reaction using Pd/Al₂O₃ as catalyst and H₂ (2.0 MPa) as reductant, led to 98% yield of target product at 120 °C in 20 h. This work provides new possibilities and routes on the sustainable synthesis of nitrogen-containing compounds from renewable biomass.

Scheme 19 (a) Reductive amination of 5-methylfurfural with aniline to yield *N*-(5-methylfurfuryl)aniline [169], (b) reductive amination of furfural derivative with ammonia [170]

6.2 Reductive amination of cyclopentanone

Cyclopentanone generated from the aqueous-phase hydrogenative ring-rearrangement reaction of furfural is a key building block for the production of medicine, rubber, perfume and high-density fuels [171,172]. The strategy of reductive amination towards synthesis of nitrogen-containing compounds was also applicable to cyclopentanone as reported by Wang *et al.* [173]. Among the nitrogen-containing derivatives of cyclopentanone, cyclopentylamine is an attractive starting material for the synthesis of medicines, cosmetics, and pesticides, and its synthesis has therefore been scrutinized [173-175]. Wang *et al.* [173] prepared Nb₂O₅ with different morphologies, such as layer Nb₂O₅ (Nb₂O₅-L), hollow Nb₂O₅ (Nb₂O₅-H) and flower-like Nb₂O₅ (Nb₂O₅-F), as carriers to support Ru nanoparticles, and used the catalysts for the reductive amination of cyclopentanone with ammonia. After carefully examination, it was discovered that 1%Ru/Nb₂O₅-L exhibited superior catalytic activity to 1%Ru/Nb₂O₅-H and 1%Ru/Nb₂O₅-F, affording 84.3% yield of cyclopentylamine with complete cyclopentanone conversion under the conditions of 90 °C, 2.0 MPa H₂ and 4 h. The as-prepared Nb₂O₅-L, Nb₂O₅-H and Nb₂O₅-F were subjected to comprehensive characterisation including XPS analysis, CO-titration and DRIFT-MS techniques to rationalize those differences in activity. The obtained results demonstrated that the superior activity of Nb₂O₅-L was strongly associated with the highest surface area of Nb₂O₅-L material rather than the electronic effect of Ru species. The highest surface area of 1%Ru/Nb₂O₅-L catalyst contributed to the highest Ru dispersion, which in turn made a significant effect on improving its catalytic performance [173]. In addition to cyclopentylamine and imine intermediate, some by-products detected in the reaction mixture stemmed from hydrogenation or aldol condensation of cyclopentanone as well as condensation of cyclopentanone with cyclopentylamine, as illustrated in Scheme 20. Moreover, the applied catalytic system was extended to various aldehydes/ketones capable of offering good yields (60-90%) towards the corresponding target products [173].

Scheme 20 Reaction pathway for the reductive amination of cyclopentanone into cyclopentylamine [173]

Recently, an inexpensive Ni/Al₂O₃ material prepared from Ni-based complexes and γ -Al₂O₃ by wet impregnation, pyrolysis and reduction methods, was verified to serve as an effective and reusable catalyst for the reductive amination of cyclopentanone with ammonia (aqueous solution) [174]. Cyclopentylamine was achieved in an excellent yield of 99% at 80 °C with 1.0 MPa H₂ and a reaction time of 20 h. In addition, many structurally diverse aldehydes and ketones could react with cyclopentanone smoothly over Ni/Al₂O₃ catalyst to afford the corresponding primary amines in good yields. Furthermore, the Ni/Al₂O₃ catalyst was also effective with bioactive compounds and natural products to yield target primary amines [174]. Additionally, other inexpensive catalyst such as Eco-Mn[®], synthesized from thermal treatment of leaves of *Grevillea exul rubiginosa* and subsequent treatment with diluted hydrochloric acid, was also highly active in the reductive amination of cyclopentanone with aniline, giving 97% yield of the corresponding target product under the conditions of 110 °C and 4 h using the safe Hantzsch ester as reductant [175].

6.3 Reductive amination of glycolaldehyde

Glycolaldehyde is a renowned bio-based platform molecule which can be synthesised from retro-aldol reaction of glucose under subcritical hydrothermal conditions [176, 177]. Glycolaldehyde shows promise as a key starting material raw for the synthesis of many interesting and important industrial chemicals, such as ethylene/propylene glycols, ethanolamine, glyoxal, formic acid, glycolic acid and tetrose sugars [178-180]. Among them, ethanolamine is a crucial chemical with an annual demand of over two million tons [181]; and the most attractive application of ethanolamine is application as an absorbent for CO₂ and SO₂ sequestration in power plants.

Reductive amination of glycolaldehyde represents one of important routes towards ethanolamine synthesis. Zhang *et al.* [181] reported an effective methodology for the reductive amination of glycolaldehyde with ammonia (25 wt% aqueous ammonia) using Ru/ZrO₂ as catalyst, furnishing 94% yield of ethanolamine at 85 °C with 2.0 MPa of H₂ in 12 h (Scheme 21). As evident from results of *in situ* catalyst characterisation, Ru/ZrO₂ functioned as a bifunctional catalyst with strong Lewis acidic sites and metallic sites due to the co-existence of multivalence Ru species (*i.e.*, Ru⁰ and RuO₂). The outstanding catalytic performance of Ru/ZrO₂ resulted from the synergistic effect of metallic Ru and RuO₂, where the imine intermediate formation took place over RuO₂ species with Lewis acidic sites through activating the carbonyl group of glycolaldehyde while the hydrogenation of imine into ethanolamine occurred in the presence of metallic Ru sites [181]. The authors had a try for the direct synthesis of ethanolamine using cellulose as starting feedstock through sequential hydrolysis and retro-aldol condensation with a two-step approach (Scheme 21). Typically, cellulose was first converted to glycolaldehyde in 20.6% yield in hot water over H₂WO₄ catalyst; then the collected reaction mixture was concentrated followed by addition of aqueous ammonia and Ru/ZrO₂ catalyst and subsequent reacted at 85 °C for 12 h allowing an overall ethanolamine yield of 10% to be attained. In addition, Ru/ZrO₂ was rationalised to be a durable catalyst as it could be reused multiple times almost maintaining its original activity [181]. This two-step conversion approach was the first example for direct synthesis of ethanolamine from cellulose and open up a

promising route towards sustainable production of ethanolamine from biomass. Furthermore, the introduced approach had a good level of generality towards reductive amination of diverse biomass-derived aldehydes or ketones, highlighting the usability of the established strategy.

Scheme 21 Reaction pathway for synthesis of ethanolamine from reductive amination of glycolaldehyde or cellulose [181]

6.4 Reductive amination of biomass-derived acids

Various carboxylic acids including lactic acid [182], succinic acid [183], glucaric acid [184], xylaric acid [185], itaconic acid [186] and formic acid [187] can be obtained from biomass-derived carbohydrates in high yields. Amongst these, lactic acid stands out due to the high market demand of biodegradable poly(lactic acid) and its function as a versatile intermediate for the production of many commodity chemicals [188,189]. An innovative strategy associated to a reductive amination route was pioneered by Yan and co-workers [190] to transform lactic acid into alanine in ammonia aqueous, whereby Ru nanoparticles supported on carbon nanotubes (Ru/CNT) and gaseous H_2 (1.0 MPa) were used as catalyst and reductant, respectively. Alanine was obtained in a high yield of 62% under the conditions of 220 °C and 2 h. In contrast, other noble metals such as, *e.g.* Pd, Pt, Rh and Ir supported on CNT showed inferior activity relative to Ru, illustrating the significant role of Ru nanoparticles in the reaction. Results from assenting experiments demonstrated the superior activity of Ru to be attributed to a reversible enhancement effect of NH_3 on the Ru nanoparticles [190]. Hence, on the basis of catalytic tests, the authors claimed

that the reaction pathway for synthesis of alanine from reductive amination of lactic acid followed a sequence of dehydrogenation, amination and reduction, as described in Scheme 22a, in which the dehydrogenation was the rate-determining step. With an attempt to directly convert glucose into alanine, a two-step strategy containing the transformation of glucose into lactic acid over $\text{Ba}(\text{OH})_2$ and subsequent reductive amination of lactic acid over Ru/CNT was applied [190]. Eventually, 43% yield of alanine was obtained in this two-step transformation, comparable to the results obtained from state-of-the-art microbial cultivation process. In addition to lactic acid, the authors also evaluated the activity of Ru/CNT in the reductive amination of other biomass-derived α -hydroxyl acids into corresponding α -amino acids such as *e.g.*, α -aminobutyric acid, valine, leucine and aspartic acid (Scheme 22b). Encouragingly, the corresponding α -amino acids were attained in promising yields (27-66%) [190], making the established protocol opening up a novel avenue for chemical transformation of biomass-derived platform molecules into essential amino acids needed for humans.

Scheme 22 (a) Synthesis of alanine from reductive amination of lactic acid and (b) reductive amination of biomass-derived α -hydroxyl acids [190]

Another attention-drawing biomass-derived acid is itaconic acid, which has great potential in the synthesis of novel and biodegradable polymers, including polyitaconates and related co-polymers [191,192]. The reductive amination of itaconic acid has been reported to selectively produce pyrrolidones. One prominent example is on a Ru/C catalyst reported by Palkovits *et al.* [193] that converted itaconic acid into *N*-unsubstituted pyrrolidones with ammonia (0.5 MPa) as nitrogen source and gaseous H₂ (15 MPa) as reductant, reaching a total yields of 83% towards 3-methylpyrrolidone and 4-methylpyrrolidone at 200 °C after 4 h of reaction time. According to the distribution of the detected products/intermediates with varying the reaction time, a plausible reaction pathway involving successive dehydrogenation, amination, cyclisation and hydrogenation was proposed (Scheme 23). Additionally, reductive amination of bio-based succinic acid into *N*-methyl pyrrolidinone or 2-pyrrolidinone using 2.5 %Rh + 2.5 %Re/C as catalyst was also reported [194].

Scheme 23 Plausible reaction pathway for the reductive amination of itaconic acid with ammonia to yield 3- and 4-methyl-2-pyrrolidone [193]

6.5 Reductive amination of carbohydrates

The main components of lignocellulosic biomass are carbohydrates in form of polymers. For example, xylan belongs to the most common hemicelluloses abundant in hard wood and perennial plants [195], and most catalytic research focuses on the transformation of xylan into small organic molecules. In addition, xylan is also a natural biopolymer, which can be upgraded into polysaccharide block copolymers or

nonionic compounds with excellent surfactant properties through functional group modification or carbon chain elongation [195,196]. One such example, is the reaction of xylan with *n*-propylamine via reductive amination process in the presence of NaBH₃CN to give modified xylan followed by reacting with unmodified xylan to afford polysaccharide block copolymers (Scheme 24a) [197]. The described work clearly pointed out reductive amination as a promising approach towards effective transformation of bio-based carbohydrates into value-added chemicals.

Besides, sucrose derived isomaltulose could be also converted into a series of nonionic compounds with excellent surfactant properties via reductive amination process with *n*-dodecylamine as shown in Scheme 24b [198]. This work highlighted that an effective catalytic system capable of facilitating the reductive amination of isomaltulose with *n*-dodecylamine was helpful to reduce our dependence on petrochemical resources in surfactant industry. Therefore, the use of the reductive amination approach is believed to bring enormous opportunities in sugar chemistry, polymer and fine chemical industry.

Scheme 24 (a) Synthesis of polysaccharide block copolymers from reductive amination of xylan [197], (b) synthesis of nonionic compounds with excellent surfactant properties from reductive amination of isomaltulose [198]

6.6 Reductive amination of bio-based fermentation products

Apart from the above biomass derivatives, various products are accessible from lignocelluloses via fermentation methods [199]. Acetone, butanol and ethanol (ABE) can be efficiently obtained from the renowned fermentation process of lignocelluloses [200,201]. Great effort has been made in the reductive amination of ABE fermentation products in the recent years [71, 202-204].

Ingleson *at al.* have developed a metal-free catalytic strategy to yield *N*-isopropylaniline from reductive amination of acetone with aniline over $B(C_6F_5)_3$ using hydrosilane (Me_2PhSiH) as reductant (Scheme 25) [71], resulting in 95% yield of *N*-isopropylaniline at 100 °C after 1.5 h. An advantage of the established protocol

is that $B(C_6F_5)_3$ was tolerant of the *in situ* formed water during the reaction due to the reversibly deprotonation of $H_2O-B(C_6F_5)_3$. An innovative method to one-pot synthesize unsymmetric tertiary amines through the reductive amination of two types of alcohols was reported by Shi and co-workers [202]. As illustrated in Scheme 25, *N*-benzyl-*N*-butylaniline was generated from the simultaneously reductive amination of butanol and benzyl alcohol with aniline over a simple $CoAlO_x$ catalyst prepared by hydrothermal method. Up to 83% yield of *N*-benzyl-*N*-butylaniline was attained over $Cu_2Al_3O_x$ (molar ratio of Cu to Al is 2:3) under the conditions of 160 °C and 24 h. Moreover, the authors discovered that different aliphatic alcohols were amenable to the reductive amination methodology to yield various unsymmetric tertiary amines, strongly demonstrating the high adaptability of the established methodology.

Ethylamine originating from ethanol via reductive amination has been of great interests recently owing to its high value in pharmaceuticals, textile chemicals and rubbers [203]. The reaction route to produce ethylamine from the reductive amination of ethanol involves dehydrogenation, condensation followed by hydrogenation (Scheme 25). Shin and co-workers described a series of Ni-supported (Ni/Al_2O_3) catalysts for the synthesis of ethylamine from reductive amination of ethanol operating in a fixed-bed reactor [204]. Attributed to the highest metallic Ni dispersion along with the smallest Ni particle size, $Ni(10\text{ wt\%})/Al_2O_3$ catalyst showed the highest catalytic performance providing about 14% yield of ethylamine (190 °C, $WHSV = 0.9\text{ h}^{-1}$).

Scheme 25 Synthesis of nitrogen-containing compounds from the reductive amination of acetone/butanol/ethanol [71, 202, 204]

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DOI: 10.1039/D0GC01869D

6.7 Reductive amination of fatty acids/triglycerides

Fatty acids and triglycerides represent a significant class of compounds in biomass-derived bio-oils and their upgrading occupies a core position in the synthesis of renewable biodiesel [205, 206]. In particular, the reductive amination of fatty acids/triglycerides has been proposed to be a promising protocol to produce fatty amines with carbon chain lengths ranging from C8 to C22, which find wide use in the chemical industry, including coating, corrosion inhibition, anti-caking and emulsification [207].

The reductive amination of fatty acids to fatty amines involves as a first step the generation of amide intermediates via reaction with ammonia followed by dehydration of amides to give nitrile intermediates and subsequent hydrogenation into fatty amines (Scheme 26) [208]. It is more challenging to convert fatty acids into fatty nitriles compared to hydrogenation of fatty nitriles into fatty amines, thus the transformation of fatty acids into fatty nitriles has received much attention. For example, various metal oxides including ZnO, Ga₂O₃, MgO, Al₂O₃, In₂O₃, SnO and Nb₂O₅ were examined to catalyze the conversion of fatty acids into fatty nitriles [208]. ZnO was found to exhibit superior catalytic performance to other metal oxides at 300 °C after 8 h, furnishing a high 97.6% yield of fatty nitriles. Subsequently, the formed fatty nitriles could be hydrogenated to yield fatty amines over metallic sites such as Pd/C, Ru/C, Pt/Al₂O₃ and Ni-based catalysts [209, 210]. Very recently, a green and effective catalytic system based on cheap ruthenium-tungsten bimetallic materials was developed for the one-pot reductive amination of various fatty acids to fatty amines by Vos and Coeck [211], furnishing excellent selectivity (70-99%) toward the corresponding fatty amine under the conditions of 200 °C, 5 MPa H₂ and 6.5 h.

Analogous to fatty acids, triglycerides has also been applied with success in the

synthesis of fatty nitriles [212]. Generally, the synthesis of fatty nitriles from triglycerides proceed by two parallel reactions: (i) triglycerides are firstly hydrolyzed to fatty acids and then follow the reaction route of fatty acids-to-fatty nitriles; (ii) triglycerides are directly converted to fatty amides followed by dehydration into fatty nitriles (Scheme 26) [212]. Viamajala and co-workers reported an innovative method for one-step vapor-phase thermocatalysis of triglycerides into fatty nitrile over many heterogeneous solid acid catalysts (*i.e.*, V_2O_5 , Fe_2O_3 , ZrO_2 , ZnO , Al_2O_3 , CuO and H-ZSM-5) at a NH_3 flow rate of 8.9 mL/mol [212]. V_2O_5 with high acidity showed superior activity relative to other tested heterogeneous solid acid catalysts, leading to 84 wt% (relative to feed mass) yield of fatty nitrile at 400 °C with a residence time of 10 s. The described methodology is very practical and energy-efficient due to the elimination of the energy-intensive triglyceride hydrolysis.

Scheme 26 Reaction pathway for the synthesis of fatty amines via reductive amination of fatty acids/triglycerides [208, 212]

6.8 Synthesis of nitrogen-containing compounds from bio-based amino acids or biopolymers

Various nitrogen-containing compounds are accessible from the reductive amination of biomass-derived oxygenated chemicals as discussed above. Nevertheless, many nitrogen-containing materials are contained in biomass, such as *e.g.*, amino acids (obtained from fermentation of biomass or isolated from protein waste hydrolysates) and biopolymers, which also represent an important class of starting feedstocks for

the synthesis of nitrogen-containing compounds [213, 214]. Several representative examples concerning the production of nitrogen-containing compounds from bio-based amino acids or biopolymers are also summarized in this review.

Vos and co-workers developed a chemocatalytic, metal-free approach for the synthesis of primary amines starting from amino acids via decarboxylation in 2-propanol [215]. They reported that many primary amines could be efficiently obtained with excellent yields (>98%) from various amino acids, including glycine, alanine, valine, leucine, isoleucine and norleucine in the presence of isophorone as catalyst under mild conditions (150 °C) (Scheme 27a). The reaction mechanism is probably correlated to the formation of Schiff base between the amino acids and isophorone. In addition, the approach was identified to tolerate an extensive substrate scope, fully demonstrating that isophorone served as a powerful organocatalyst for the decarboxylation of amino acids. Interestingly, the authors found that formamides were predominant products when the reactions were conducted in dimethyl formamide, which was ascribed to the formed amines consecutive undergoing *N*-acylation facilitated by the acidity of the amino acids [215]. Lysine, as the most abundant amino acid industrially produced from biomass fermentation, encompasses two amino groups showing great potential as a feedstock towards the production of nitrogen-containing compounds [216]. The synthesis of caprolactam (an important monomer for nylon-6 polymer production) from lysine was demonstrated by Zhang and co-workers [217]. 29.6% yield of caprolactam was attained over Ir/H-Beta bifunctional catalyst under the conditions of 250 °C, 2 h and 2.0 MPa H₂, wherein the acidic sites on the Ir/H-Beta catalyst facilitated the formation of lactam while the synergy of acidic sites and metallic sites promoted C-N hydrogenolysis to yield caprolactam. Additionally, the superiority of Ir/H-Beta catalyst was correlated with the large pores of H-Beta, which accommodated intermediate molecules inside the pores during the reaction. The reaction route toward caprolactam from lysine was determined to follow cyclization, *N*-methylation and subsequent hydrogenolysis pathway, involving α -dimethyl amino caprolactam as an intermediate (Scheme 27b)

[217]. Importantly, diamines with widely application in polyamides production could also be synthesized from lysine (Scheme 27b) [218]. A recent example of synthesis of diamine from lysine via deoxygenation was reported by Lin and co-workers using the combination of Ru/C and phosphoric acid, giving 100% lysine conversion with 51% yield of 1,5-diaminohexane at 200 °C with 2 h and 2.8 MPa of H₂ [218].

Scheme 27 (a) Synthesis of amines from decarboxylation of amino acids [215], (b) transformation of L-lysine into caprolactam or 1,5-diaminohexane [217, 218]

Besides amino acids, many biopolymers, such as *e.g.*, polynucleotides, chitin and melanin, contain abundant nitrogen as element. Particularly, chitin, as the most abundant nitrogen-bearing polysaccharide in biomass and a prominent component in shells of crustaceans/insects, is considered a promising feedstock for the synthesis of nitrogen-containing compounds [219]. As a nitrogen-containing derivative of chitin, *N*-acetyl glucosamine represents a privileged compound with widely application in pharmacology, food and cosmetics industry [220]. Yan *et al.* reported an efficient acidified lithium halide molten salt hydrate system comprising 60 wt% LiBr and 40

mmol HCl for the conversion of chitin into *N*-acetyl glucosamine, affording 71.5% yield of *N*-acetyl glucosamine at 120 °C with 0.5 h (Scheme 28a) [221]. By combined ¹³C NMR and ATR-FTIR analysis, the authors claimed that Li ions substantially altered the hydrogen-bonding network of chitin, which subsequently resulted in enhanced polymer dissolution/swelling thereby facilitating the chitin-to-*N*-acetyl glucosamine transformation [221].

Chitosan, derived from chitin via deacetylation, also serves as a promising starting material for the production of nitrogen-containing compounds. Glucosaminic acid is a versatile molecule with great potential in the synthesis of sweetener, condiment and pharmaceuticals [222], and it has been produced from chitosan via tandem hydrolysis and oxidation as described by Yan and co-workers (Scheme 28b) [23]. The tandem transformation of chitosan into glucosaminic acid was achieved by the combination of Amberlyst-15 and Au/MgO via a two-step process, where chitosan was initially hydrolyzed into glucosamine (58% yield based on chitosan) in the presence of Amberlyst-15 at 160 °C within 2 h, and subsequently the formed glucosamine (after detoxication by removal of humins with activated carbon) was oxidized into glucosaminic acid (63% yield based on glucosamine) over Au/MgO under the conditions of 40 °C, 0.5 MPa O₂ and 3 h. This work provides inspiration for the selectivity synthesis of nitrogen-containing compounds from nitrogen-containing biopolymers. Actually, various nitrogen-containing biopolymers are contained in inedible biomass, and it is expected that diverse nitrogen-containing compounds could be selectivity produced from those biopolymers.

Scheme 28 (a) Reaction pathway for the synthesis of *N*-acetyl-glucosamine from chitin [221] and (b) reaction pathway for the conversion of chitosan into glucosaminic acid [23]

7 Conclusions and perspectives

In summary, reductive amination constitutes a very promising approach to access useful nitrogen-containing compounds from renewable biomass derivatives. Various reducing agents including gaseous hydrogen, formic acid, hydrosilane and NaBH_4 together with many elegant methods have been recently developed for the reductive amination of bio-based platform molecules. Moreover, the past decade has also witnessed a rapid development in innovative catalysts, efficient catalytic systems and diverse reaction pathways for reductive amination of bio-based molecules. Recent advances in the reductive amination of biomass-derived platform molecules have in this review been summarised with emphasis on several renowned platform molecules such as *e.g.*, furfural, HMF, levulinic acid and lignin-based model monomers. A major focus has further been put on the state-of-the-art catalysts, structure-reactivity relationships, reaction pathways, catalytic mechanism, catalyst durability and generality.

For continued research of reductive amination of bio-based molecules, some

suggestions can be proposed aiming of accelerating the process of industrial production, in spite of significant achievements in this area.

(i) An essential step in the reductive amination is the reduction of imine intermediates to amines, and the usage of reductants is here an important aspect due to its importance in terms of the safety, greenness and operability of the whole process. Apart from the current most applied reductants (*i.e.*, gaseous hydrogen, formic acid, hydrosilane and NaBH_4), the development of other green reductants such as alcohol and water can contribute to increasing the sustainability of production as well as improving the market competitiveness.

(ii) Both noble- and non-noble catalysts are active for the reductive amination, however, non-noble metal-based catalysts generally require harsher reaction conditions to reach satisfied results compared to noble metal-based catalysts. The development of effective non-noble metal-based catalysts thus deserves more attention. In particular, several emerging protocols (*e.g.*, ultra-fine metal particle dispersion technology, single-atom technology and advanced methods of fabricating porous hierarchical structure), capable of efficiently contributing to the improvement of catalytic performance, may be extended to novel non-noble metal-based catalysts applied for reductive amination of bio-based molecules. Besides, attention should also be paid on green preparation methods of catalysts (*e.g.*, mechanochemical methods and development of magnetic catalysts as well as biomass-based catalysts), which further reinforce the sustainability and greenness of production.

(iii) Reductive amination of lignin-based model monomers is still in the early-stage research, and early work have primarily focused on commercial or modified Pd/C catalysts. Therefore, there is great potential for the development of innovative effective catalysts, preferable non-noble metal-based catalysts, for reductive amination of lignin-based model monomers.

(iv) Current strategies for reductive amination of bio-based molecules mainly involve the usage of ammonia or organic amines as nitrogen source. Some organic amines (*e.g.*, aspartic acid and glutamic acid) stemming from biomass should not be neglected as well. Using bio-based amines as nitrogen source for the reductive

amination of bio-based molecules actually makes the protocol more attractive and allows more diverse kind of nitrogen-containing compounds to be made.

(v) Green catalytic systems based on photo- or electrochemistry can be extended to applications in the reductive amination of biomass-derived molecules. These strategies may bring enormous opportunities for developing various novel, effective catalysts for reductive amination, and exert a positive impact on pushing the processes towards industrialisation.

(vi) Reductive amination is generally a cascade reaction involving multiple reaction processes, making it is very essential to illuminate the corresponding reaction pathway and reaction mechanism. Several advanced technologies, including *in situ* NMR and *in situ* characterisation of active sites, are greatly conducive in helping elucidating the evolution of reactions and roles played by catalysts during reactions and such methods can be utilized in reductive amination. In addition, multistep kinetic studies along with theoretical calculations based on DFT and molecular energetics can also help to crisply understand the rate-determining step as well as reaction mechanisms.

(vii) Most research to date have concentrated upon batch reactions with small volumes for investigating reductive amination. In contrast, continuous flow strategy with fixed-bed reactors affords fascinating advantages such as *e.g.*, improved thermal management, improved mass, energy efficiency and scalability as well as larger volumes, showing great potential for large-scale industrial application. Thus, employing continuous flow strategy for reductive amination deserves more attention.

(viii) Based on the view that bio-based molecules originates from biomass-derived carbohydrates, future focus should be shifted to directly use bio-based carbohydrates, or even lignocellulosic biomass, as starting materials for the synthesis of nitrogen-containing compounds. The key for achieving this goal is designing innovative integrated processes composed of efficient transformation of carbohydrates into platform molecules, and subsequent efficiently facilitating reductive amination of the bio-based molecules into nitrogen-containing compounds. Such integrated catalytic system is less energy-intensive and features better economics by reducing

chemical wastes, organic solvents, and operation steps. Particular attention is expected directed to the achievements in creative design of effective integrated catalytic process.

Acknowledgement

JH acknowledges the Outstanding Youth Project of Hunan Provincial Education Department (19B470) for funding this work. SL acknowledges sponsorship of the open project of Key laboratory of Hunan Forest Product and Chemical Industry Engineering (No. LCHG1903). SY acknowledges the National Natural Science Foundation of China (No. 21576059) for financial support.

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View Article Online
DOI: 10.1039/D0GC01869D

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Graphical abstract

The latest studies in synthesis of nitrogen-containing compounds from various bio-based platform molecules, including furfural, 5- hydroxymethylfurfural, levulinic acid and lignin model monomers, are systematically summarized and discussed in this review.