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The role of N-containing carbohydrates in organic catalysis: a review

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The utilization of carbohydrate biomass in organic catalysis is central to the development of sustainable chemical feedstocks and biologically active compounds, yet efforts have largely focused on oxygenated biopolymers, leaving N-containing carbohydrates (NCCs), such as chitin, chitosan, and D-glucosamine, relatively underexplored. Despite their abundance, biocompatibility, and inherent chirality, NCCs remain an untapped class of renewable nitrogen-rich materials with transformative potential in green and asymmetric catalysis. The lack of a focused, comprehensive analysis of their role in organic catalysis has limited the integration of NCCs into mainstream organic synthesis. Here, we critically review recent progress in the application of NCCs as (1) renewable feedstocks to produce value-added chemicals *via* regioselective C–N, C–C, and C–O bond cleavage; (2) chiral ligands in metal-catalyzed asymmetric transformations; and (3) organocatalysts for enantioselective organic chemical reactions. These developments reveal that NCCs are versatile molecular scaffolds capable of replacing fossil-based inputs in sustainable organic catalysis. We further outline emerging frontiers that could define the next decade of research. These directions represent high potential strategies to unlock new chemical reactivity, enhance stereocontrol, and extend the utility of NCCs across synthetic, medicinal, and materials chemistry. This review positions NCCs as key enablers in the transition toward renewable, precision-driven molecular science.

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1. While previous reviews have focused primarily on oxygenated saccharides, this work fills a critical gap by systematically analyzing the role of nitrogen-containing carbohydrates (NCCs) as feedstocks, ligands, and organocatalysts in organic catalysis.
2. This area of study is of broad and growing significance due to its intersection with several high priority research domains, including biomass valorization, sustainable catalysis, and asymmetric synthesis. The unique structural attributes of NCCs, such as their dense functionality, inherent chirality, and stereochemical diversity, position them as ideal building blocks for sustainable chemical transformations.
2. These insights are expected to inspire the development of novel catalytic methodologies, stimulate cross-disciplinary collaboration, and promote the replacement of fossil-derived reagents with sustainable alternatives. This review helps position NCCs at the core of green chemistry innovation, driving both fundamental discovery and practical application in catalysis, synthetic chemistry, and biomaterials science.

1. Introduction

Biomass, a renewable organic resource derived from plants, microorganisms, and animals, stores solar energy in the form of chemical bonds.[1] Over the past decade, extensive research has focused on the (bio)chemical valorization of the carbon-, hydrogen-, and oxygen-containing components of biomass, such as carbohydrates, lignin, triglycerides, proteins, DNA, and RNA, into biofuels, materials, and fine chemicals.[1–16] In stark contrast, NCCs, notably chitin, chitosan, and D-glucosamine, have received significantly less attention, despite being widely available, structurally unique, and functionally rich.[16–18] This underutilized class of NCCs holds great promise, especially in the context of the global shift away from fossil resources. As fossil feedstock becomes increasingly scarce and environmentally unsustainable, the development of sustainable, nitrogen-rich alternatives is imperative. Chitin, the second most abundant natural polysaccharide after cellulose, is primarily obtained from the exoskeletons of crustaceans and fungal cell walls.[15,19,20] It consists of *N*-acetyl-D-glucosamine and D-glucosamine units linked by β-(1 → 4) glycosidic bonds, with a degree of acetylation greater than 50%. Chitosan, derived from chitin by deacetylation, contains less than 50% *N*-acetylated units and exhibits distinct solubility and reactivity properties.[21–23] Hydrolyzed monomers such as D-glucosamine (GlcN) and *N*-acetyl-D-glucosamine (GlcNAc) further expand the chemical utility of this family.

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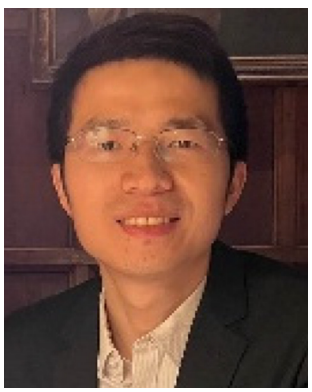
Beyond their biological relevance and wide use in biomedicine, food chemistry, and environmental science due to their biocompatibility, biodegradability, and antimicrobial activity,[24–31] NCCs offer unique opportunities for application in organic catalysis. Their molecular structures feature multiple modifiable functional groups (*e.g.*, amino and hydroxyl groups at the C2, C3, and C6 positions) and, crucially, an inherently chiral backbone, a feature that is highly desirable for asymmetric synthesis. In the pharmaceutical and fine chemical industries, the efficient synthesis of chiral molecules is of critical importance. Asymmetric catalysis, a key strategy in this context, often relies on synthetic chiral ligands or catalysts, which are typically expensive and derived from non-renewable sources. In contrast, NCCs provide a sustainable and cost-effective alternative, serving either as chiral auxiliaries or as organocatalysts in stereoselective reactions. Their natural abundance, chemical versatility, and built-in chirality make them ideal candidates to support sustainable and green asymmetric catalysis. Although carbohydrate-based catalysis has been reviewed in recent years, the focus has largely been on oxygenated saccharides. To date, there exists no comprehensive review dedicated to NCCs in organic catalysis, leaving an important gap in the literature. This review seeks to fill that void by systematically summarizing the emerging roles of chitin, chitosan, and D-glucosamine derivatives in catalytic organic transformations. In section 2, we highlight the use of these *N*-carbohydrates as feedstocks, emphasizing regioselective activation strategies to cleave C–N, C–C, C–O bonds to transform them into valuable small molecules. In section 3, we discuss their application as ligands in metal-catalyzed asymmetric transformations, focusing on how both natural and chemically tailored chiral centers influence stereoselectivity and catalytic performance. In section 4, we review their use as organocatalysts, particularly aminocatalysts and bifunctional thiourea/urea–amine derivatives, evaluating their impact on enantioselectivity (ee values) and reaction yields. By bringing together these three perspectives, this review aims to inspire broader interest in this underdeveloped area and stimulate future research. We hope to demonstrate that NCCs are not only sustainable alternatives to fossil-based catalysts and ligands but also powerful enablers of green and asymmetric synthesis. Finally, we provide a critical outlook on the future directions and potential breakthroughs in the field.



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2. N-Containing carbohydrates as feedstocks for N-containing chemicals

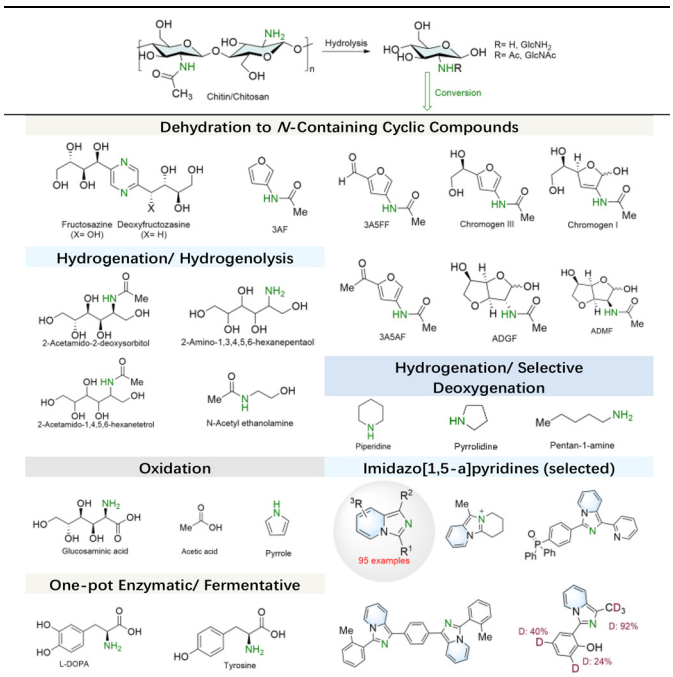
Despite chitin being one of the most abundant biopolymers on Earth, human utilization of chitin-containing raw materials, such as crustacean shells, represents only a small fraction of the total chitin produced annually in nature.[32–37] The vast majority of natural chitin remains unutilized and decomposes in the environment.[38] In contrast, low molecular weight nitrogen-containing compounds play an essential role in pharmaceuticals, agriculture, food, and materials science.[16,39–41] Industrially, the nitrogen source for the synthesis of nitrogen-containing compounds is predominantly derived from ammonia (NH_3), nitrate (NO_3^-), and nitrite (NO_2^-), which are themselves produced through energy-intensive nitrogen fixation processes, primarily the Haber–Bosch process.[42–46] Remarkably, the amount of nitrogen naturally fixed into chitin *via* biological processes is estimated to be significantly greater than the nitrogen fixed by the Haber–Bosch process on an annual basis.[5] This striking contrast has sparked growing interest in valorizing renewable, nitrogen-rich chitin biomass as a sustainable feedstock for the production of value-added chemicals.[16] Such strategies not only enable the circular use of bio-based nitrogen resources, but also offer a greener alternative to conventional fossil-based and energy-intensive pathways.

To date, few strategies are currently known for the activation of chitin/chitosan.[47–50] The strategy that involves direct modifications of amines on the chitosan/chitin backbones to prepare bio-based functional materials is one of the main routes toward activation of these biomass.[35] Another strategy relies on strong oxidants or strong acidic conditions to cleave C–N bonds in chitin/chitosan, simultaneously releasing N_2 or limited types of organic and primarily inorganic low-value chemicals, such as acetamide and ammonium salts.[51] These two strategies cannot generate value-added small molecular chemicals, in particular more complex organic compounds, which are highly desired in modern life. For the utilization of N-containing carbohydrates, such as chitin and chitosan, as feedstocks for value-added small molecular compounds, the process mainly involves hydrolysis to first produce the monomers $GlcNH_2$ and GlcNAc.[53–56] On the other hand, $GlcNH_2$ and its derivatives, such as glucosamine hydrochloride, glucosamine sulfate, and GlcNAc, are widely used as nutraceuticals for osteoarthritis relief. Traditional production methods often

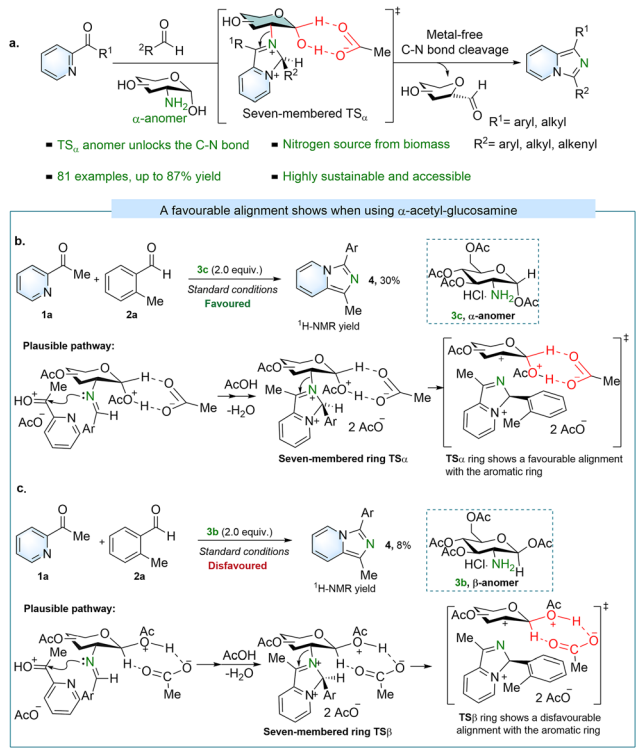
rely on seafood waste and toxic chemicals, raising environmental and allergen concerns. Recent advances focus on eco-friendly bio-based approaches, including enzymatic chitin hydrolysis, fungal biotransformation, and engineered microbial systems for sustainable GlcN and GlcNAc production.[57] Here, we have not discussed oligosaccharides of chitin and chitosan.[58,59] These monomers are further modified into value-added products (Table 1), such as hydrogenation to prepare alcohols (2-acetamido-2-deoxysorbitol, 2-amino-1,3,4,5,6-hexanepentaol, 2-acetamido-1,4,5,6-hexanetetrol, and *N*-acetyl ethanolamine),[60–62] dehydration to synthesize nitrogen-containing cyclic compounds (3AF, 3A5AF, 3A5FF, fructosazine, deoxyfructosazine, chromogen III, chromogen I, ADGF, and ADMF),[63–73] oxidation to obtain carboxylic acid compounds (glucosaminic acid, acetic acid, and pyrrole),[51,74,75] dehydration–deamidation to prepare nitrogen-free aromatics (5-HMF, FMF, and 5-chloromethylfurfural),[76–80] enzymatic/fermentative methods for the preparation of amino acid derivatives (L-DOPA and tyrosine),[5] hydrogenation/selective deoxygenation for the preparation of nitrogen-containing chemicals (piperidine, pyrrolidine, and pentan-1-amine),[81] and selective C–N bond cleavage for the preparation of imidazo[1,5-*a*]pyridines[82,83] (Table 1). The mechanism of each type reaction has been reviewed.[16,84] More importantly, several representative reviews have so far summarized the methods for preparing value-added nitrogen-containing chemicals.[47,49,50,85–89] Biorefinery strategies have emerged involving the conversion of chitin/chitosan into a preliminary C6 backbone *via* depolymerization (*e.g.* monomeric and oligomeric molecules) followed by the conversion of the C6 backbone into diverse products *via* cleavage and rearrangement.[5,16] For example, in 2020, Yan and Zhou *et al.* reported a biorefinery process to upgrade shell waste-derived chitin to tyrosine and L-DOPA through an integrated process.[5] The process includes pretreatment of chitin-containing shell waste and an enzymatic/fermentative bioprocess using metabolically engineered *Escherichia coli*. Although various protocols have been established through enzymatic, catalytic and/or hydrothermal treatments pathways, only about 17 examples (including sugar derivatives, amino alcohols, nitrogen-containing cyclic compounds, amino acid derivatives, and furanic amides) have been obtained under complicated conditions and with low efficiency. In 2016, a strategy involving the cleavage of the C–N bond of chitin for the assembly of pyrrole with a low yield of 4% was reported. It was realized in an alkali aqueous solution at 300 °C.[75] Nikahd *et al.* exploited chitin as a source of biologically fixed nitrogen for the preparation of a group of small-molecule hetero- and carbocyclic pyrolysis products at 150–350 °C.[90] They developed diverse pathways to obtain specific value-added compounds, including 2-methylbenzo[*d*]oxazol-6-ol, 2-acetamidocyclopent-2-en-1-one, 3-acetamido-6-methyl-2*H*-pyran-2-one, 3-acetamido-2*H*-pyran-2-one, and (*E*)- and (*Z*)-3-acetamido-5-ethylidenefuran-2(5*H*)-one. In particular, it should be stressed that the synthesis of N-heterocycles from chitin/chitosan biomass is challenging and introducing an external nitrogen source is the main pathway for the construction of N-heterocycles from biomass.[91,92] The C–N bond of chitin/chitosan that offers a potential reactive site for various versatile chemical diversifications generally remains underutilized. Therefore, the development of one-pot protocols enabling the targeted efficient incorporation of nitrogen from chitin/chitosan into diverse valuable chemicals like N-heterocycles is highly attractive, which will advance the existing methodologies while expanding the library of N-containing chemicals derived from renewable sources.

Imidazo[1,5-*a*]pyridines are an important class of nitrogen-containing heterocycles with wide-ranging applications in pharmaceutical chemistry, coordination chemistry, and materials science.[93–98] They serve as precursors of N-heterocyclic carbenes,[96–98] ligands in transition metal complexes,[95,99] and inhibitors of biologically active targets.[93,94] However, prior to recent developments, there were no efficient methods to synthesize imidazo[1,5-*a*]pyridines from NCCs *via* regioselective C–N bond cleavage, limiting the utilization of renewable carbohydrate-based biomass in this area. Carbohydrates have garnered increasing attention as chiral auxiliaries in stereoselective synthesis[100,101] and for their role in stereocontrol of transition-metal complexes *via* the metallo-anomeric effect.[102] In aqueous solution, D-glucosamine exists in equilibrium between α- and β-anomers, with their relative abun-

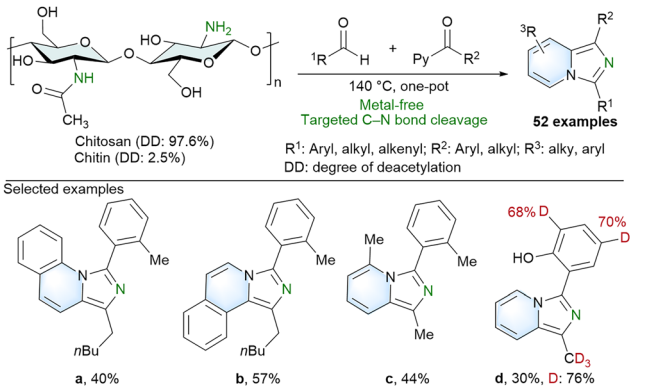
Table 1 Synthesis of diverse value-added chemicals from chitin, chitosan and D-glucosamine



ADGF = 2-acetamido-3,6-anhydro-2-deoxyglucofuranose; ADMF = 2-acetamido-3,6-anhydro-2-deoxymannofuranose; 3-3A5FF = acetamido-5-formylfuran; 3A5AF = 3-acetamido-5-acetylfuran; 3AF = 3-acetamidofuran; 5HMF = 5-hydroxymethylfurfural; FMF = 5-(formyloxymethyl)furfural; L-DOPA = L-3,4-dihydroxyphenylalanine. R^1: aryl, alkyl, alkenyl; R^2: aryl, alkyl; R^3: alky, aryl. Reproduced from ref. 52 with permission from the PhD thesis available in eDiss (open access), copyright 2022.



Scheme 1 Anomeric stereoauxiliary cleavage of the C–N bond of D-glucosamine for the preparation of imidazo [1,5-*a*] pyridines. Reproduced from ref. 82 with permission from Wiley-VCH GmbH, copyright 2022.



Scheme 2 Direct nitrogen interception from chitin/chitosan for imidazo [1,5-*a*] pyridines. Reproduced from ref. 83 with permission from the Royal Society of Chemistry, copyright 2022.

dance modulated by pH and other factors.[38,103] Inspired by this anomeric behavior, Zeng *et al*. developed a novel method to exploit the α-anomer of D-glucosamine for C–N bond cleavage, enabling the direct construction of imidazo[1,5-*a*]pyridine derivatives (Scheme 1).[82] This transformation proceeds through the formation of a seven-membered ring transition state, a non-covalent interaction unique to the α-anomer (Scheme 1b), that facilitates selective C–N bond cleavage under acidic aqueous conditions at 120 °C, without requiring any metal catalysts or external nitrogen sources. This mechanistic pathway was supported by ESI-MS analysis, density functional theory (DFT) calculations, and control experiments. Using this innovative strategy, the authors synthesized over 83 examples of imidazo[1,5-*a*]pyridine derivatives from a broad range of pyridine ketones (including *para*-disubstituted dipyridine ketones) and aldehydes (including *para*-dialdehydes). Notably, this protocol also enabled the efficient preparation of deuterium-labeled imidazo[1,5-*a*]pyridines, incorporating both C(sp^2)–D and C(sp^3)–D bonds, which are of significant value in drug metabolism studies and isotope labeling applications. This work highlights the potential of carbohydrate-based stereoauxiliaries in controlling reactivity and selectivity, offering a novel and practical approach for the construction of complex nitrogen-containing heterocycles. Beyond D-glucosamine, Zeng *et al.* further extended this approach to polysaccharide feedstocks, including chitosan and chitin, developing a catalyst-free, one-pot method for the synthesis of imidazo[1,5-*a*]pyridines directly from these renewable nitrogen-rich biomaterials (Scheme 2).[83] This protocol enabled the preparation of 52 examples of imidazo[1,5-*a*]pyridines under mild conditions, achieving yields of up to 92%. The products include 1-alkyl-substituted derivatives (39 examples) and 1-aryl-substituted derivatives (13 examples), many of which were inaccessible using traditional methods. This work represents a significant advancement in the valorization of NCCs, establishing a general, metal-free route to access value-added N-heterocycles from abundant, renewable biomass with high functional group tolerance and a broad substrate scope.

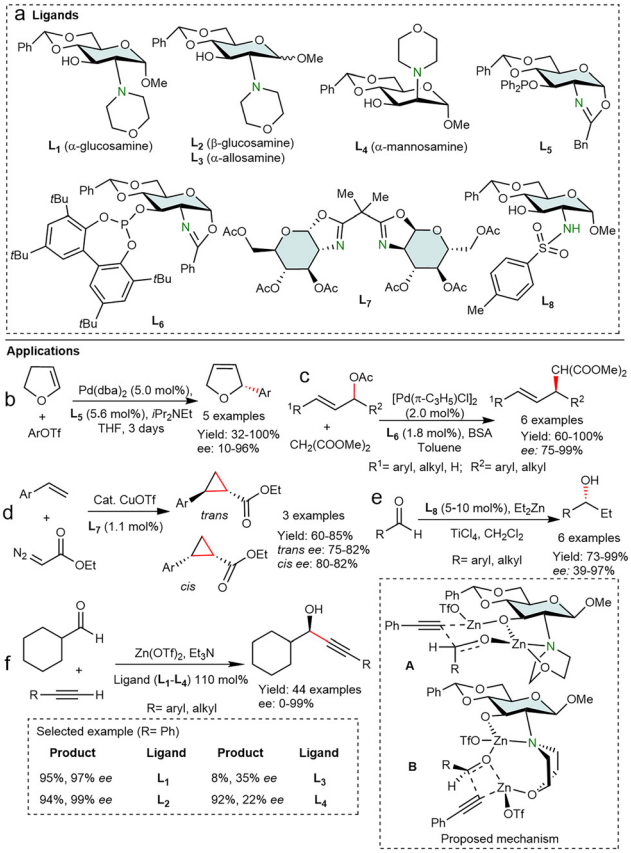
In addition to the synthesis of nitrogen-containing compounds, NCCs can also serve as sustainable feedstocks for the production of commercially important bulk chemicals, which are typically derived from fossil resources. Li *et al.* developed an electrocatalytic strategy for the efficient conversion of chitin into acetic acid and green hydrogen.[51] This process involves the initial depolymerization of chitin to *N*-acetyl-D-glucosamine (GlcNAc), followed by its electrooxidation. The hybrid electrolysis system achieved over 90% yield of acetate, while simultaneously generating H_2 gas as a valuable byproduct. This approach offers a clean and energy-efficient alternative for producing both acetic acid and hydrogen from biomass. In the same year, Chen *et al.* reported a switchable and selective oxidation method for converting GlcNAc into various organic acids under ambient conditions.[104] Using molecular oxygen (O_2) as the oxidant in dilute NaOH, the reaction selectively yielded acetic acid and glyceric acid. When hydrogen peroxide (H_2O_2) was employed as the oxidant instead, the major product was formic acid. Compared to traditional methods that typically require high temperatures and pressures, this room-temperature approach is safer, more economical, and environmentally friendly, demonstrating the potential of carbohydrate-based biomass for the green production of platform chemicals.

3. N-Containing carbohydrates as ligands in organic catalysis

Enantiomerically pure compounds play crucial roles in the pharmaceutical, agrochemical, and flavor industries.[105] These chiral molecules can be synthesized through various methodologies, including organometallic catalysis, enzymatic transformations, and organocatalysis. Enantioselective homogeneous metal catalysis remains one of the most attractive and widely applied strategies. In recognition of their groundbreaking contributions to this field, W. S. Knowles, R. Noyori, and K. B. Sharpless were jointly awarded the 2001 Nobel Prize in Chemistry. In this enantioselective catalysis, the use of chiral ligands is fundamental. These ligands coordinate to metal centers and create an asymmetric chiral environment that enables the selective transformation of prochiral substrates into chiral products. Thus, the rational design and selection of appropriate chiral ligands is a critical factor influencing both the reactivity and stereocontrol of the catalytic system. Over the years, numerous chiral ligands have been developed, significantly expanding the diversity of accessible structures and enabling the fine-tuning of enantioselectivity in a wide range of asymmetric transformations.[106,107]

Carbohydrates, the most abundant and renewable class of biomolecules, possess natural chiral backbones and have emerged as valuable scaffolds for the construction of chiral ligands in asymmetric catalysis.[100,108,109] Unlike many synthetic ligands, carbohydrate-based ligands are economical and readily available, and do not require multistep installation of stereocenters, making them attractive for sustainable and cost-effective synthesis. Carbohydrate-derived ligands have been widely employed in various enantioselective transformations,[100,108–111] and numerous reviews have covered sugar-based ligands designed for phosphine, phosphinite, and phosphite architectures.[100,108,109,112–114] These ligands have demonstrated broad utility in asymmetric hydrogenation, hydroformylation, allylic substitution, 1,4-addition, Heck reactions, hydroboration, hydrosilylation, and cyclopropanation. In this section, we focus on chitin, chitosan, and their monomeric derivatives as ligand precursors for enantioselective transformations in organic synthesis, highlighting their structural advantages, coordination behavior, and application scope.

Natural chitin, chitosan, and amino sugars possess inherent nucleophilicity due to the presence of amino groups, which render them more chemically reactive than non-nitrogenous carbohydrates. Their amino functionalities enable facile derivatization, allowing for the design of tailored ligands for use in asymmetric catalysis and other organic transformations (Scheme 3a).[115,116] Kunz *et al.* were the first to utilize D-glucosamine in the synthesis of a phosphine–oxazoline (PHOX) ligand scaffold.[117] This design was later improved by Uemura *et al.*, who incorporated a diphenylphosphinite group, enhancing its performance in asymmetric allylic substitution reactions.[118,119] The resulting ligand **L5**, featuring a phosphinite–oxazoline structure, was subsequently employed in



Scheme 3 Representative examples of ligands derived from amino sugars and their applications. $Pd(dba)_2$ = bis(dibenzylideneacetone)palladium; BSA = *N*,*O*-bis(trimethylsilyl)acetamide; ee = enantiomeric excess. Reproduced from ref. 52 with permission from the PhD thesis available in eDiss (open access), copyright 2022.

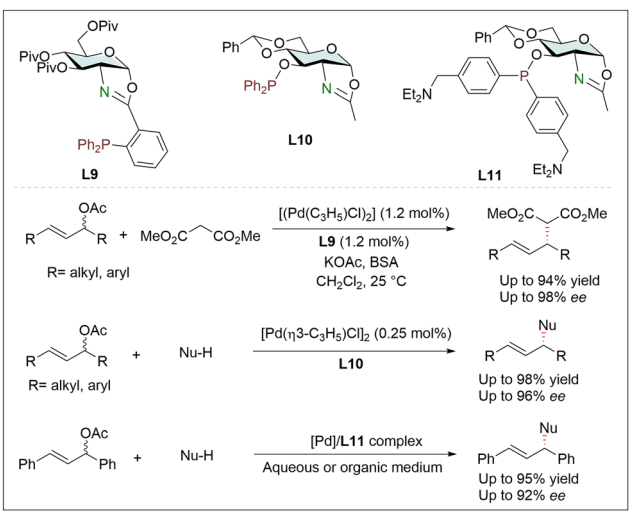
Pd-catalyzed asymmetric Heck reactions and in the enantioselective arylation of 2,3-dihydrofuran using aryl triflates as electrophiles (Scheme 3b).[120]

Further contributions include the work by Boysen *et al.*, who developed a C_2-symmetric bis(oxazoline) ligand **L7**, also derived from D-glucosamine, and successfully applied it in copper-catalyzed cyclopropanation of styrene with diazoacetate (Scheme 3d).[121] In a similar context, Bauer *et al.* designed ligand **L8**, which demonstrated high enantioselectivity and yield in the addition of diethylzinc to aldehydes (Scheme 3e).[122] In 2005, Diéguez *et al.* introduced a novel family of phosphite–oxazoline ligands (**L6**), which were readily accessible and effective in palladium-catalyzed asymmetric allylic substitution reactions (Scheme 3c).[123] A set of amino sugar-derived ligands (**L1–L4**) were investigated as chiral additives in the diethylzinc addition to aldehydes (Scheme 3f).[124] Ligands **L1** (α-anomer) and **L2** (β-anomer) both delivered excellent yields and enantioselectivities, suggesting that anomeric configuration has minimal influence on the reaction outcome. In contrast, **L3** (α-allosamine) led to low yield and ee, while **L4** (α-mannosamine) gave high yield but low ee. These results indicated that the C3-hydroxyl group plays a pivotal role in

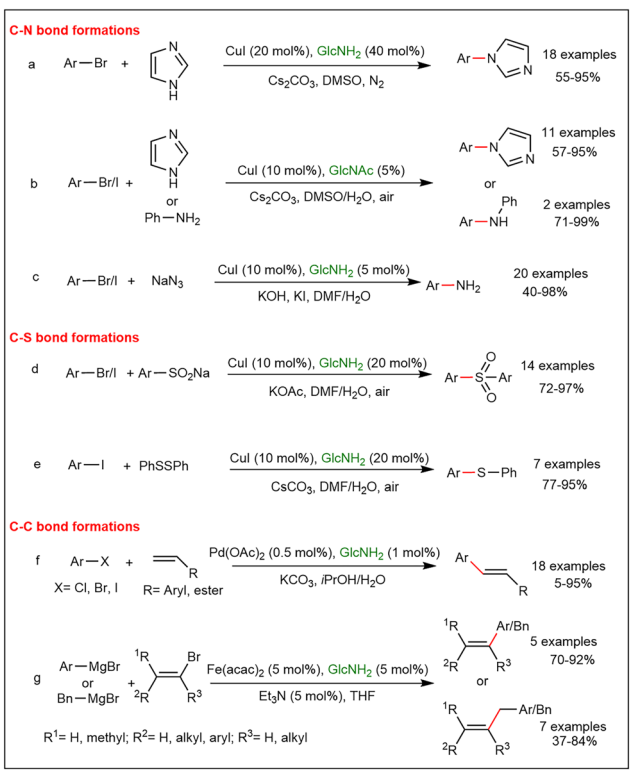
achieving high yields, while the C2-amino group is key to controlling enantioselectivity. Based on these observations, the authors proposed a mechanistic model involving the formation of a five-membered chelate ring through coordination between the C2-amino group, a hydroxyl group (likely at C3), and zinc, thereby stabilizing the chiral transition state and enhancing stereoselectivity.

Glucosamine can be chemically modified to incorporate phosphite functionalities, enabling the synthesis of novel chiral ligands with high stereodifferentiating potential. For instance, a novel enantiomerically pure ligand, 2-[2-(diphenylphosphino)phenyl]-4,5-(2-deoxy-α-D-glucopyrano)-oxazoline (**L9**), was synthesized from glucosamine (Scheme 4).[117] The effectiveness of **L9** was demonstrated in palladium-catalyzed intermolecular allylic substitution reactions of both symmetrically and non-symmetrically substituted allyl acetates, affording products with high yields and excellent enantioselectivities (up to 98% ee). Building on this concept, Yonehara *et al.* developed a series of palladium-catalyzed asymmetric allylic substitution reactions employing novel chiral phosphinite–oxazoline ligands (**L10**) derived from D-glucosamine.[118] These ligands exhibited high catalytic efficiency and afforded allylic alkylation and amination products with substantial enantiomeric excess. For example, the allylic alkylation of 1,3-diphenyl-3-acetoxyprop-1-ene with dimethyl malonate proceeded smoothly in the presence of 0.25 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and **L10** bearing the smallest oxazoline substituent at 0 °C within 6 hours, yielding the product with 96% ee. Hashizume *et al.* reported the synthesis of a novel water-soluble amphiphilic chiral ligand (**L11**) derived from D-glucosamine, which was successfully applied in palladium-catalyzed asymmetric allylic substitution reactions conducted in either aqueous or organic media.[120] The resulting catalyst complex, [Pd]/**L3**, specifically, [Pd(2-methyl-4,5-[4,6-*O*-benzylidene-3-*O*-bis[(4-((diethylmethylammonium)methyl)phenyl)]phosphino-1,2-dideoxy-α-D-glucopyranosyl]-[2,1-*d*]-2-oxazoline)$(\eta^3\text{-}C_3H_5)]^{3+}\cdot 3BF_4^-$, exhibited good water solubility and functioned efficiently in water or aqueous/organic biphasic systems, achieving enantioselectivities of up to 85% ee. This catalytic system offers practical advantages, including easy separation of the aqueous catalyst phase from the organic product phase and the ability to recycle the catalyst multiple times without significant loss of activity or selectivity, highlighting its potential for sustainable and green asymmetric catalysis.

In addition to its well-established role as ligands in asymmetric catalytic organic synthesis, D-glucosamine has also proven effective as a ligand in metal-catalyzed transformations that do not involve the creation of chiral centers, such as various cross-coupling reactions.[125] Bao *et al.* reported the use of D-glucosamine as a ligand in Ullmann-type copper-catalyzed *N*-arylation of imidazoles with both aryl and heteroaryl bromides (Scheme 5a).[126] This work demonstrated the potential of naturally derived carbohydrate ligands in promoting C–N bond formation. Building upon this foundation, Zhou *et al.* significantly improved the method in 2016 by employing *N*-acetylglucosamine (GlcNAc) as the ligand under aerobic conditions, and further expanded the substrate scope from imidazoles to aromatic amines (Scheme 5b).[127] Theoretical studies suggested that the hydroxyl groups at the C3, C4, and C6 positions of GlcNAc played a key role in the coordination with the



Scheme 4 Representative examples of ligands derived from amino sugars and phosphite functionalities and their applications in asymmetric catalysis.



Scheme 5 Construction of C–N, C–S and C–C bonds *via* metal-catalyzed reactions with the ligand D-glucosamine. Fe(acac)$_2$ = iron(II) acetylacetonate. Reproduced from ref. 52 with permission from the PhD thesis available in eDiss (open access), copyright 2022.

copper catalyst and in modulating the catalytic cycle. However, the specific influence of the C1-hydroxyl group and C2-amino group remains unexplored and warrants further investigation. In 2011, Sekar *et al.* utilized D-glucosamine as a ligand in the copper-catalyzed azidation of aryl halides, enabling the selective synthesis of anilines from aryl halides and sodium azide (NaN_3) (Scheme 5c).[128] Subsequently, in 2014, Zhang *et al.* reported that D-glucosamine served as an efficient ligand in the copper-catalyzed synthesis of aryl sulfones from aryl halides and sodium sulfinates (Scheme 5d).[129] They further extended this strategy to the cross-coupling of diphenyl disulfides with aryl iodides using CuI in the presence of glucosamine as a ligand (Scheme 5e).[130] Beyond copper catalysis, D-glucosamine has also proven effective in other metal-catalyzed systems. It has been employed in palladium-catalyzed Mizoroki–Heck reactions involving aryl halides (Scheme 5f)[131] and in iron-catalyzed Grignard-type cross-coupling reactions with vinylic and allylic bromides (Scheme 5g).[132] These examples collectively highlight the versatility and utility of D-glucosamine and its derivatives as environmentally friendly, readily available chiral ligands for a broad spectrum of transition-metal-catalyzed cross-coupling reactions.

4. N-Containing carbohydrates as organocatalysts in organic catalysis

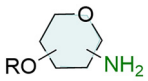
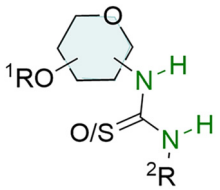
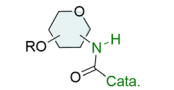
Organic catalysis represents a transformative strategy in modern chemical synthesis, playing an essential role in numerous global chemical production processes. Within this domain, asymmetric catalysis has garnered significant attention due to its ability to selectively generate specific enantiomers, an outcome of particular importance in drug discovery and development. The enantioselective synthesis of complex molecules not only improves therapeutic efficacy but also reduces off-target effects. Traditional approaches for asymmetric catalysis primarily involve metal complexes with chiral ligands. While effective, these methods often require strictly anhydrous or anaerobic reaction conditions and rely on expensive and sometimes toxic metal catalysts. Such limitations significantly hinder their scalability and industrial application. Alternatively, enzymatic catalysis offers high stereoselectivity under mild conditions, but its broader utility is restricted by substrate specificity, high cost, and the need for delicate reaction environments. In response to these challenges, researchers have pursued catalytic systems that combine wide substrate tolerance, high selectivity, and environmental compatibility. This pursuit culminated in the emergence of organocatalysis, a concept popularized by David W. C. MacMillan and Benjamin List in the early 2000s. For instance, MacMillan demonstrated enantioselective Diels–Alder reactions *via* iminium activation,[133] while List utilized proline to promote asymmetric aldol reactions through enamine catalysis.[134] Although aldehydes are inherently more electrophilic and generally react faster than ketones with aminocatalysts like proline to form iminium intermediates, the aldol reaction is intentionally designed so that the aminocatalyst first reacts with the ketone. In this catalytic cycle, the ketone serves as the nucleophile precursor, condensing with the aminocatalyst to generate an enamine intermediate, while the aldehyde is reserved as the electrophile. This selectivity is achieved by reaction design, typically using an excess of ketone, controlling the order of addition, and relying on the aldehyde's higher electrophilicity to ensure it reacts preferentially with the enamine rather than competing for aminocatalyst binding. As a result, even though aldehydes might outcompete ketones under unbiased conditions, the aldol reaction conditions channel the aminocatalyst's reactivity toward the ketone first, enabling efficient C–C bond formation with the aldehyde. These covalent activation strategies, particularly enamine and iminium catalysis, have since evolved into powerful tools in synthetic chemistry, inspiring a wave of innovation across diverse reaction types.[135–141]

Today, organocatalysis is a thriving area of research,[142–145] with a broad array of catalyst classes expanding its scope from fine chemicals to pharmaceuticals and natural product synthesis.[142,146–156] Representative organocatalysts include cinchona alkaloids,[157] proline,[133] imidazolidinones,[134] diarylprolinol silyl ethers,[158] and notably, carbohydrates.[159] Among these, carbohydrates, owing to their abundance, biocompatibility, and innate chirality, have emerged as attractive scaffolds for the development of novel organocatalysts. In particular, NCCs such as chitin, chitosan, and D-glucosamine have drawn increasing interest. These compounds share a common glucosamine backbone and offer versatile points for functionalization, enabling the creation of structurally diverse and catalytically active materials. Chitin, the second most abundant natural polymer, is widely found in crustacean shells and fungal cell walls. Its deacetylated derivative, chitosan, and its monomeric unit, D-glucosamine, are not only biodegradable and non-toxic but also exhibit excellent solubility and reactivity, making them ideal candidates for organocatalyst design. This section focuses on recent advancements in the use of NCCs as organocatalysts, particularly emphasizing three major classes (Table 2): (a) aminocatalysts, (b) carbohydrate-derived urea/thiourea–amine catalysts, and (c) other types of organocatalysts. Through this lens, we aim to highlight how these naturally occurring molecules are being leveraged to address longstanding challenges in asymmetric synthesis while aligning with the principles of green chemistry and sustainability.

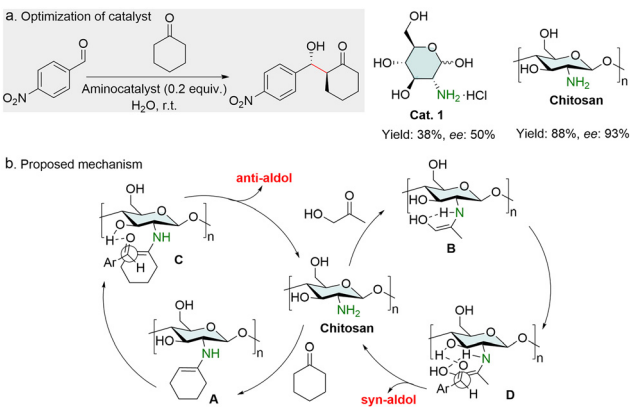
4.1. N-Containing carbohydrate-derived aminocatalyst

Representative aminocatalysts such as cinchona alkaloids, L-proline, imidazolidinones, and diarylprolinol silyl ethers have played a pivotal role in the development of asymmetric aminocatalysis. These well-established organocatalysts have demonstrated broad utility across a variety of enantioselective transformations. Recently, the incorporation of NCCs as chiral aminocatalysts has further enriched the field, offering a sustainable and structurally diverse alternative to traditional, often synthetically demanding, aminocatalyst systems. In a notable example, K. Rajender Reddy *et al.* developed a chito-

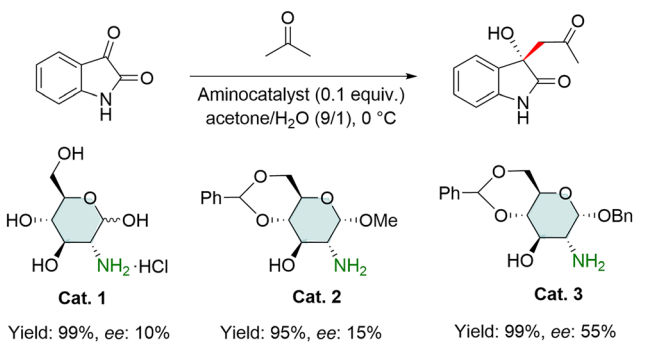
Table 2 Summary of the reaction type and mechanism based on N-containing carbohydrates as organocatalysts

Organocatalysts	Reaction type	Key mechanisms	Ref.
 Aminocatalysis R= H, alkyl, Bn	Aldol reaction	*Via* enamine	160–162
	Michael addition	*Via* enamine	163
	Mannich reaction	*Via* enamine	164
	Baylis–Hillman reaction	*Via* iminium ion/enamine tandem sequence and anomeric stereoauxiliary	165
 Urea/Thiourea-amines Bifunctional Catalyst R^1= Ac, H R^2= alkyl amine	Michael addition	*Via* enamines or enol	166–169
	Biginelli reaction	*Via* enamine	170
	Aldol reaction	*Via* enamine	171
	Oxa-Michael–Michael cascade	*Via* enol	172
	Mannich reaction	*Via* enol	173–175
	Nucleophilic addition	*Via exo*-anomeric effect	110, 168 and 176
 Other type of Organocatalysis Cata.= phosphinyl, carboxyl etc. R= H, Ac	Morita Baylis–Hillman reaction	*Via* enol	177
	Aldol reaction	*Via* enamine	178

san-based hydrogel as a green and recyclable biopolymer catalyst for aldol and Knoevenagel reactions.[179] These transformations proceeded efficiently under biphasic conditions, affording products in excellent yields and with high chemoselectivity. Importantly, the hydrogel catalyst could be recovered by simple filtration and reused multiple times with minimal loss of catalytic activity, demonstrating its robustness and practical applicability. In another significant contribution, Alfredo Ricci and colleagues introduced chitosan aerogel microspheres as recyclable, heterogeneous organocatalysts for the asymmetric direct aldol reaction in water (Scheme 6).[160] The system provided aldol products in high yields, with enantioselectivities reaching up to 93% ee, and retained its activity over four successive catalytic cycles. Mechanistically, the authors proposed that chitosan's primary amine condenses with cyclohexanone to form the *E*-configured enamine intermediate **A**, whereas hydroxyacetone preferentially forms the *Z*-enamine intermediate **B**, stabilized through intramolecular hydrogen bonding. These enamines subsequently react with aldehydes, which are likely activated by hydrogen bonding with the 3-hydroxyl group of the carbohydrate scaffold, forming intermediates **C** and **D**. These pathways lead predominantly to the *anti*- and *syn*-aldol adducts, respectively. Notably, the authors also suggest the involvement of additional hydrogen-bonding interactions between the substrate and hydroxyl groups from the same or neighboring saccharide units, potentially enhancing stereoselectivity. These studies highlight the growing utility of N-containing carbohydrate-based aminocatalysts in asymmetric catalysis, showcasing their potential as renewable, recyclable, and environ-



Scheme 6 (a) Optimization of aminocatalysts for direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde. (b) The proposed mechanism.



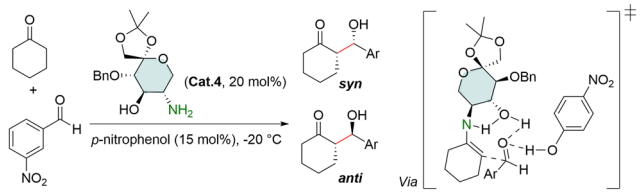
Scheme 7 Enantioselective aldol reaction of isatin with acetone catalyzed by carbohydrate-derived catalysts.

mentally benign alternatives to conventional small-molecule organocatalysts.

Inspired by the success of chitosan-based aminocatalysts, Shen *et al.* developed a series of carbohydrate-derived alcohols for use in enantioselective aldol reactions between isatins and ketones (Scheme 7).[161] Their investigation began with glucosamine hydrochloride (**Cat. 1**), which yielded aldol products with low enantioselectivity (10% ee). Protection at the anomeric position significantly improved performance, with methyl (**Cat. 2**) and benzyl (**Cat. 3**) groups increasing the ee up to 55%, with the benzyl group delivering superior stereocontrol. This enhancement was attributed to the increased steric hindrance conferred by the bulkier substituent at the anomeric position. Upon further optimization, a wide variety of isatins were successfully employed, affording aldol products in high yields (up to 99%) and with moderate enantioselectivities (up to 75% ee), underscoring the potential of protected amino sugars in asymmetric synthesis.

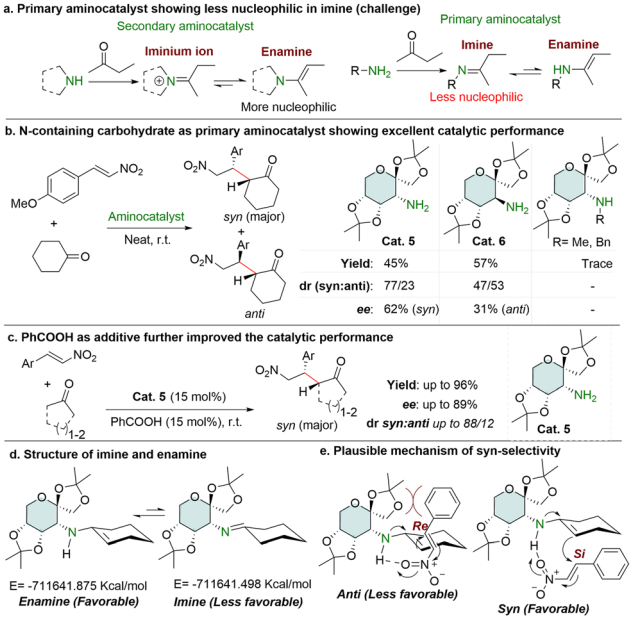
Building on these findings, Li *et al.* reported a novel catalytic system based on D-fructose-derived β-amino alcohols for direct asymmetric aldol reactions of aromatic aldehydes with cyclic ketones, utilizing *p*-nitrophenol as a co-catalyst (Scheme 8).[162] Using 20 mol% of the β-amino alcohol (**Cat. 4**) and 15 mol% of *p*-nitrophenol, the team achieved aldol products in excellent yields (up to 98%) and with good enantioselectivities (up to 87% ee). ^{1}H NMR spectroscopy was employed to probe the reaction mechanism, which is believed to involve initial enamine formation followed by C–C bond formation. Hydrogen bonding between the aldehyde's carbonyl and both *p*-nitrophenol and the hydroxyl group at C-3 of the sugar likely activates the electrophile and stabilizes the transition state, enhancing the reaction's stereocontrol and catalytic efficiency. The catalyst demonstrated good reusability with 77–84% recovery across multiple cycles.

While enamine intermediates from secondary amines are commonly employed as nucleophiles in Michael additions, reactions involving primary amines typically proceed *via* imines, which are less nucleophilic. Vanlaldinpuia *et al.* computationally investigated the feasibility of using primary aminosugars as catalysts for this transformation (Scheme 9a and



Cycle	Recovery of aminocat. (%)	Time (h)	Yield (%)	dr *syn:anti*	ee (%) *syn*	ee (%) *anti*
1	84	24	93	1:2.39	48	81
2	81	24	88	1:2.68	46	78
3	80	24	90	1:2.41	48	80
4	77	24	91	1:2.77	48	79
5	79	24	89	1:2.62	45	80

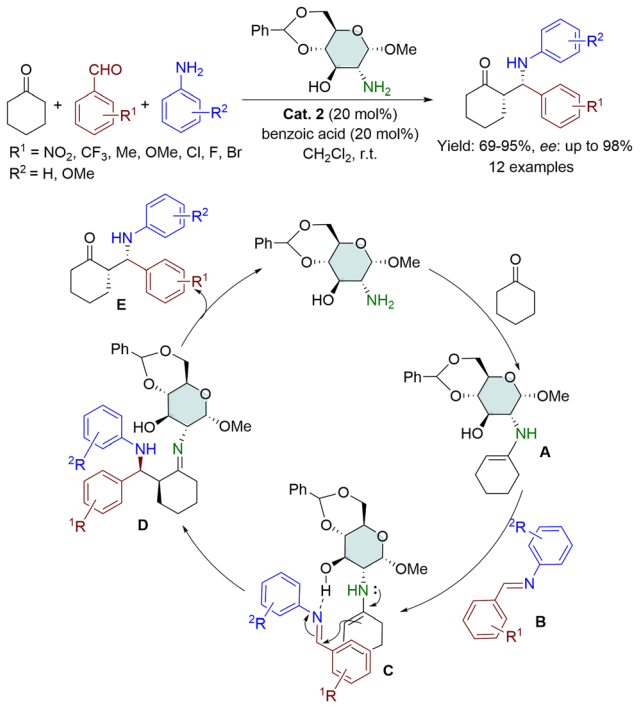
Scheme 8 D-Fructose-derived β-amino alcohols for direct asymmetric aldol reactions of aromatic aldehydes with cyclic ketones.



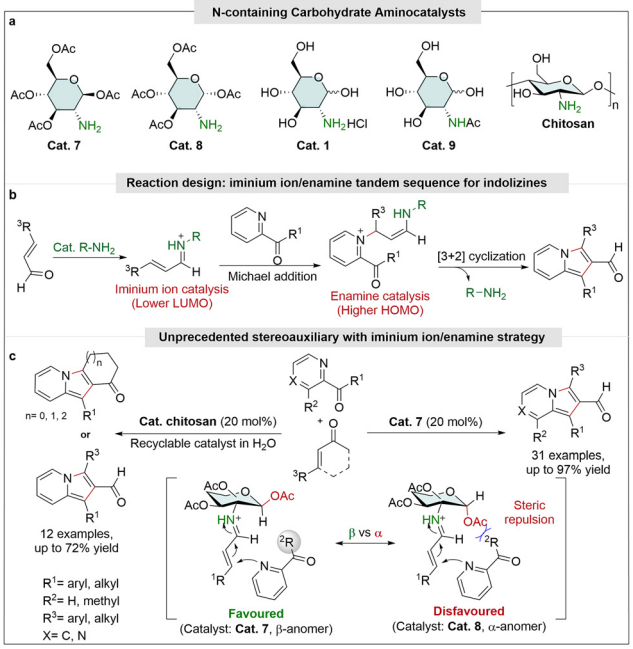
Scheme 9 Michael addition of unactivated ketones to nitroolefins catalyzed by D-fructose-derived monofunctional primary amine.

d).[163] Density Functional Theory (DFT) calculations revealed that the enamine intermediate (−711 641.875 kcal mol^{-1}) is more stable than the imine form (−711 641.498 kcal mol^{-1}), supporting its viability as a Michael donor. Subsequently, they reported the first use of a monofunctional primary amine derived from D-fructose, specifically 1,2:4,5-di-*O*-isopropylidene-3-amino-3-deoxy-α-D-fructopyranose (**Cat. 5**), as a highly effective catalyst for asymmetric Michael addition of ketones to nitroolefins (Scheme 9b). The reaction delivered up to 96% yield, 88 : 12 dr, and 89% ee, while the opposite stereoisomer (**Cat. 6**) exhibited inferior reactivity and selectivity. Modifications to generate secondary amines from the fructose framework (*via* methylation or benzylation) led to diminished activity, likely due to steric hindrance. The addition of benzoic acid as an additive significantly improved the performance, presumably by facilitating enamine formation (Scheme 9c). Under optimized solvent-free conditions with 15 mol% catalyst and 15 mol% benzoic acid, the model reaction between cyclohexanone and 4-methoxy-β-nitrostyrene gave the desired product in 86% yield, with 88 : 12 dr and 89% ee favoring the *syn*-product. The mechanism (Scheme 9e) involves hydrogen bonding between the NH of the enamine and the nitro group of the nitroalkene, orienting the *Si*-face of the olefin below the enamine plane to direct *syn*-selective bond formation.

In a related study, Sharma *et al.* developed the first direct asymmetric Mannich reaction catalyzed by a D-glucosamine-derived β-amino alcohol (Scheme 10).[164] Optimization using cyclohexanone, aniline, and 4-nitrobenzaldehyde as substrates led to excellent outcomes: 77% yield, 12 : 1 diastereomeric ratio (*syn* : *anti*), and 98% ee using 20 mol% **Cat. 2** and 20 mol% benzoic acid in CH_2Cl_2 at room temperature. Control experiments demonstrated that the hydroxyl group at the C-3



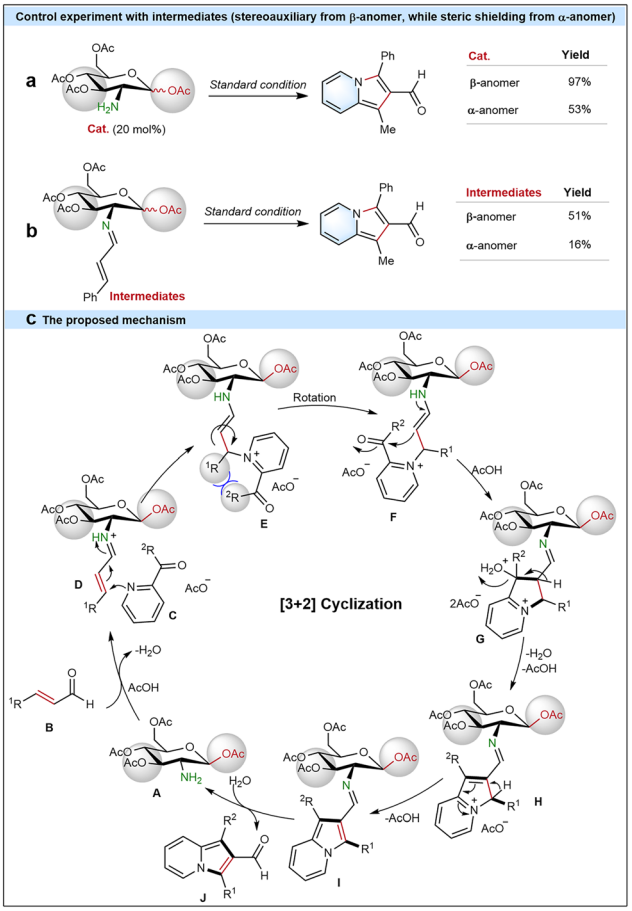
Scheme 10 Direct asymmetric Mannich reaction catalyzed by a D-glucosamine-derived β-amino alcohol.



Scheme 11 A recyclable stereoauxiliary amino-catalyzed strategy for the one-pot synthesis of indolizine-2-carbaldehydes. Reproduced from ref. 165 with permission from Springer Nature, copyright 2023.

position of glucosamine is critical for both yield and stereocontrol, activating the imine *via* hydrogen bonding and enabling *Re*-face attack by the enamine, consistent with a *syn*-selective mechanism.

Recent advances in N-containing carbohydrate-based aminocatalysis have revealed powerful strategies that leverage tandem catalysis and stereochemical control *via* carbohydrate structural elements. Among these, stereoauxiliary catalysis from the anomeric position and tandem iminium ion/enamine sequences represent two emerging approaches that dramatically expand the utility of carbohydrate-derived scaffolds in asymmetric transformations. Zeng *et al.* first introduced a novel α-anomeric stereoauxiliary strategy, utilizing D-glucosamine as a chiral reagent to promote C–N bond cleavage and the synthesis of diverse imidazo[1,5-*a*]pyridines through a seven-membered-ring transition state.[82] This approach was further extended to a catalyst-free, one-pot methodology, enabling the direct incorporation of nitrogen atoms from chitin or chitosan into target heterocycles, thereby enhancing the sustainability of the protocol.[83] These studies highlighted the potential of the anomeric center as a stereoauxiliary control element, complementing the more commonly exploited amino and hydroxyl groups on the sugar backbone. Building on this concept, in 2023, Zeng *et al.* reported a glucosamine-based β-anomeric stereoauxiliary aminocatalytic system that enabled the efficient one-pot synthesis of 1,2,3-trisubstituted indolizine-2-carbaldehydes *via* a [3 + 2] annulation of acyl pyridines and α,β-unsaturated aldehydes (Scheme 11).[165] The β-anomeric catalyst (**Cat. 7**) exhibited superior activity and selectivity compared to its α-anomeric counterpart (**Cat. 8**), due to reduced steric hindrance and favorable stereoelectronic alignment. This work also introduced the first example of a tandem iminium ion/enamine catalytic sequence using an N-containing carbohydrate scaffold. The sequential Michael–aldol cascade proceeds through a conformationally adaptive enamine intermediate, overcoming steric barriers and enabling streamlined C–C bond formation. Furthermore, polymeric chitosan, composed of β-D-anhydroglucosamine units, was demonstrated as a practical, recyclable organocatalyst under aqueous conditions, supporting sustainable, scalable synthesis of indolizine derivatives. The proposed mechanism is shown in Scheme 12. After the formation of the iminium ion/enamine tandem sequence (**D** to **E**), enamine **F** can be simply formed from **E** *via* rotation, which will overcome the bulky steric hindrance between R^1 and R^2. This new approach largely expands the scope of readily accessible indolizine-2-carbaldehydes relative to existing state-of-the-art methods. Despite the successful preparation of indolizine-2-carbaldehydes by the activation of α,β-unsaturated aldehydes, due to the electronically less active and more sterically demanding nature of α,β-unsaturated ketones toward iminium formation with an aminocatalyst, the efficient one-pot transformation of α,β-unsaturated ketones for distinct 2-acylindolizines bearing sensitive groups remains a challenge for synthetic chemists. Inspired by the stereoauxiliary strategy, in 2024, Zeng and co-workers reported a weak-coordination-auxiliary amino-catalyzed approach that enables directed [3 + 2] cyclization of α,β-unsaturated ketones and N-heteroaryl ketones to afford the desired 2-acylindolizines *via* an iminium

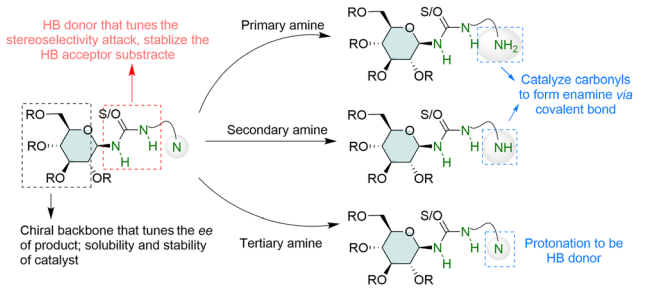


Scheme 12 Control experiments and the proposed mechanism. R^1: aryl, alkyl; R^2: aryl, alkyl. Reproduced from ref. 165 with permission from Springer Nature, copyright 2023.

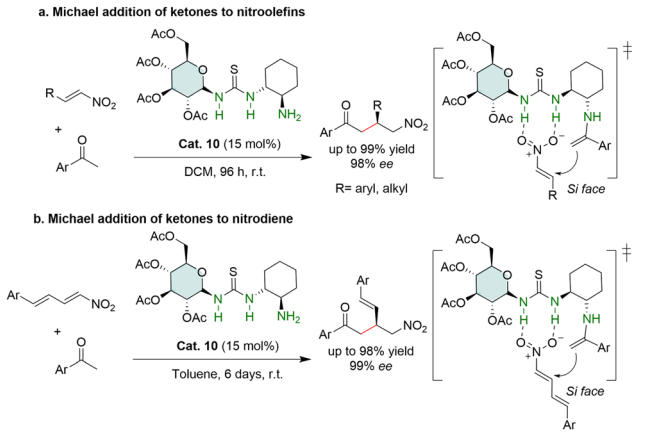
ion/enamine tandem sequence.[180] Control experiments and in-depth DFT calculations highlight the importance of the weakly coordinating glycine's carboxylic group in promoting the intramolecular cyclization and 1,5-proton transfer processes. These studies illustrate how stereoauxiliary design at the anomeric position and tandem catalysis mechanisms can be synergistically integrated into carbohydrate-based aminocatalysis. This line of work significantly enriches the synthetic toolbox for constructing nitrogen-rich heterocycles while aligning with the principles of green and sustainable chemistry.

4.2. N-Containing carbohydrate-derived urea/thiourea–amine bifunctional catalyst

Chiral thiourea and urea derivatives have proven to be extraordinarily useful as catalysts for the enantio-selective activation of carbonyl and imine derivatives toward nucleophilic addition.[181,182] NCCs are particularly attractive scaffolds due to their chiral richness, abundance, sustainability, and biocompatibility. This section discusses the development of bifunctional catalysts combining carbohydrate-derived urea/thiourea motifs with various amine functionalities (primary, secondary, and tertiary) (Scheme 13).



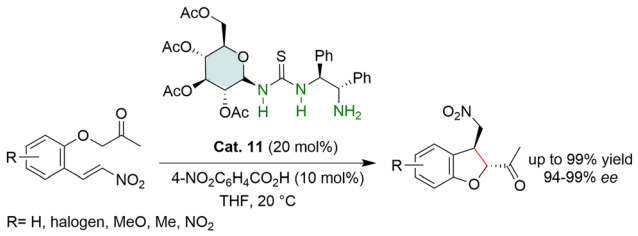
Scheme 13 Overview of the structure and role of a N-containing carbohydrate-derived urea/thiourea–amine catalyst. R: Ac, H.



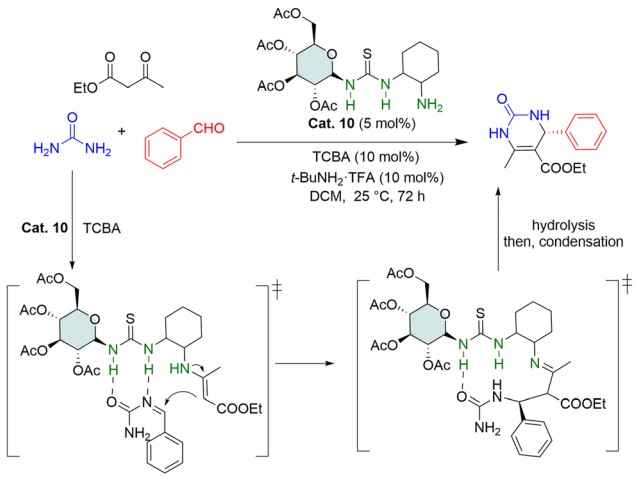
Scheme 14 The Michael addition catalyzed by a N-containing carbohydrate-derived thiourea–primary amine bifunctional catalyst.

4.2.1. N-Containing carbohydrate-derived urea/thiourea–primary amine bifunctional catalyst. Liu *et al.* reported a series of simple, yet highly effective, bifunctional thiourea–primary amine catalysts derived from saccharides for the enantioselective Michael addition of aromatic ketones to nitroolefins (Scheme 14).[166] These catalysts (**Cat. 10**) demonstrated excellent catalytic efficiency, delivering products with up to 99% yield and 98% ee. The primary amine forms an enamine intermediate with the ketone, while the thiourea moiety activates the nitroolefin through dual hydrogen bonding, stabilizing the transition state and directing stereoselectivity *via* *Si*-face attack. Building on this platform, the same group extended the substrate scope to α,β-γ,δ-unsaturated nitro compounds by utilizing nitrodienes as Michael acceptors.[183] This expansion emphasized the catalyst's broad applicability and the effectiveness of its bifunctional design in handling more challenging substrates.

Lu *et al.* advanced this concept to an intramolecular setting, using a glucosyl-based thiourea–primary amine catalyst (**Cat. 11**) for the enantioselective synthesis of *trans*-dihydrobenzofurans *via* Michael addition (Scheme 15).[167] Yields reached 99% and enantioselectivities exceeded 99% ee, demonstrating that rigid carbohydrate scaffolds can enforce high stereocontrol even in cyclic transition states. Wang *et al.*



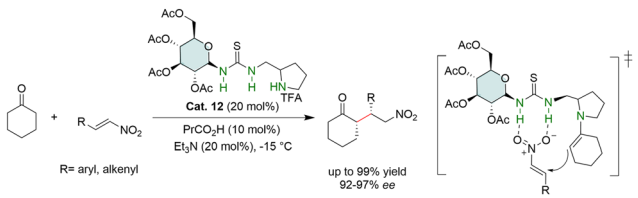
Scheme 15 Enantioselective synthesis of *trans*-dihydrobenzofurans *via* Michael addition.



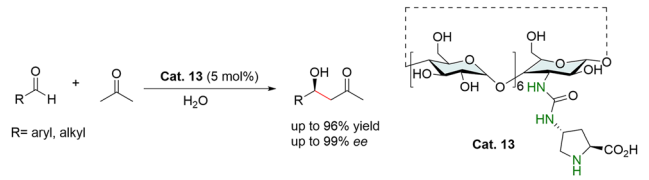
Scheme 16 Enantioselective synthesis of dihydropyrimidines *via* the Biginelli reaction.

applied a similar catalytic framework (**Cat. 10**) to the Biginelli reaction, achieving dihydropyrimidines with up to 99% ee and moderate to high yields (Scheme 16).[170] The inclusion of a Brønsted acid additive, *tert*-butylammonium trifluoroacetate (*t*-$BuNH_2$·TFA) in dichloromethane at room temperature, improved the turnover, underscoring the role of hydrogen bonding environments in modulating catalyst activity.

4.2.2. N-Containing carbohydrate-derived urea/thiourea–secondary amine bifunctional catalyst. In contrast to primary amines, secondary amine–thiourea systems enable reactions proceeding *via* classical enamine catalysis. Lu *et al.* reported a highly enantio- and diastereoselective Michael addition of cyclohexanone to nitroolefins, catalyzed by a chiral glucose-derived bifunctional secondary amine–thiourea organocatalyst



Scheme 17 The Michael addition catalyzed by a N-containing carbohydrate-derived thiourea–secondary amine bifunctional catalyst.

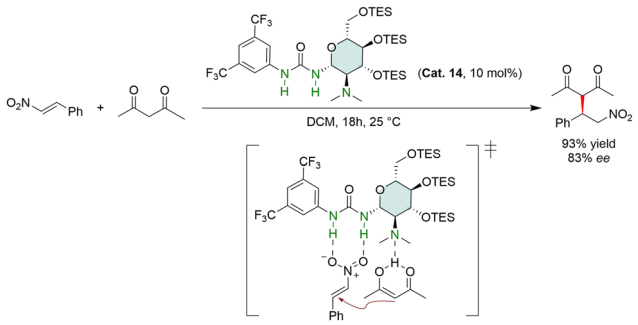


Scheme 18 Direct asymmetric aldol reactions in aqueous media catalyzed by a β-cyclodextrin–proline conjugate with a urea linker.

(**Cat. 12**) (Scheme 17).[168] To ensure the stability of **Cat. 12** during storage, 20 mol% trifluoroacetic acid (TFA) was required to suppress its slow decomposition, while 20 mol% triethylamine (Et_3N) was added *in situ* to liberate the active secondary amine species. Through extensive optimization, the best conditions were identified as 20 mol% **Cat. 12**, 10 mol% propionic acid ($PrCO_2H$), and 20 mol% Et_3N, in toluene at −15 °C. Under these optimized conditions, a broad range of Michael adducts were obtained in excellent yields, with diastereoselectivities up to >99 : 1 dr and enantioselectivities up to 97% ee. Notably, the presence of electron-donating or electron-withdrawing groups on the nitroolefins had minimal influence on the yield or stereoselectivity. A transition state model was proposed to rationalize the observed selectivity. The free base form of **Cat. 12** acts as a bifunctional catalyst: the pyrrolidine unit forms an enamine intermediate with the ketone substrate, aided by the Brønsted acid co-catalyst ($PrCO_2H$), while the thiourea moiety, along with the acid additive, activates the nitroolefin *via* hydrogen bonding. The subsequent *Re*-face nucleophilic attack of the enamine on the activated nitroolefin leads to the formation of the stereodefined Michael adduct, consistent with the experimental outcomes.

Liu *et al.* reported a direct asymmetric aldol reaction in aqueous media catalyzed by a β-cyclodextrin–proline conjugate linked *via* a urea moiety (Scheme 18).[171] Covalent attachment of proline to β-cyclodextrin through a urea linkage afforded the water-soluble chiral organocatalyst **Cat. 13** in high yield. Using 5 mol% of **Cat. 13** under aqueous conditions, asymmetric aldol condensations between acetone and a broad range of aldehydes were successfully carried out, delivering the corresponding products in moderate to high yields (up to 96%) with excellent enantioselectivities (up to 99% ee). The study also evaluated substrate selectivity, confirming the catalyst's versatility across different aldehyde structures. Importantly, recycling experiments demonstrated the excellent recyclability and reusability of **Cat. 13** without significant loss of catalytic performance over multiple cycles. This work highlights the modularity, aqueous compatibility, and environmental sustainability of carbohydrate-derived organocatalysts, reinforcing their value in green asymmetric synthesis.

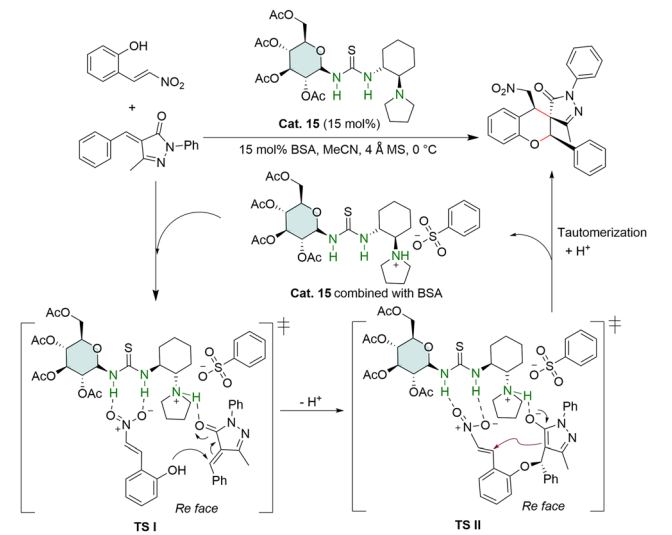
4.2.3. N-Containing carbohydrate-derived urea/thiourea–tertiary amine bifunctional catalyst. Tertiary amines, though incapable of enamine formation, serve as an effective base or hydrogen bond acceptors in bifunctional systems. Puglisi *et al.* reported carbohydrate-based urea–tertiary amine catalyst bifunctional organocatalysts (**Cat. 14**) for the stereoselective



Scheme 19 The proposed stereoselection model for acetylacetone addition to β-nitrostyrene.

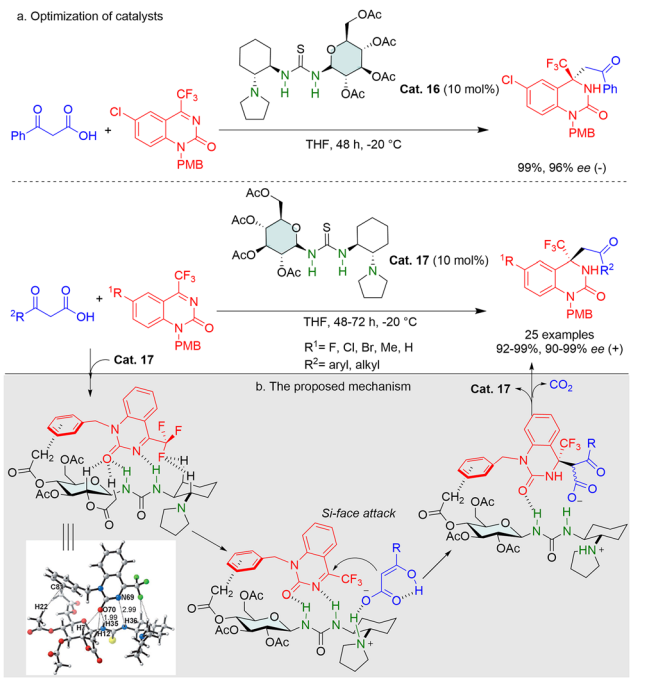
nucleophilic addition of acetylacetone to β-nitrostyrene in DCM at room temperature for 18 h, under the best conditions, obtaining enantioselectivities up to 83% (Scheme 19).[169] In the transition state, the hydroxyl group of acetylacetone interacts with the tertiary amino of the catalyst by hydrogen bonding. At the same time, the hydrogen bonding between urea as the HB donor and the nitro group as the HB acceptor also takes place. The bifunctional organocatalyst system proved that a new family of chiral bifunctional organocatalysts was successfully realized, starting from a readily available, cheap, enantiomerically pure material such as D-glucosamine.

Zheng *et al.* developed an efficient strategy for the asymmetric synthesis of spiro[chroman-3,3′-pyrazol] scaffolds bearing an all-carbon quaternary stereocenter *via* an oxa-Michael–Michael cascade reaction catalyzed by bifunctional amine–thiourea organocatalysts (**Cat. 15**) (Scheme 20).[172] This transformation proceeds under low catalyst loading (15 mol% of **Cat. 15**) and affords the desired products in high to excellent yields (up to 98%), with moderate to high enantioselectivities (up to 99%) and diastereoselectivities (up to 20 : 1). The methodology offers a streamlined and stereocontrolled route to access chiral spiro[chroman-3,3′-pyrazol] derivatives featuring three contiguous stereocenters, which are of potential pharmaceutical relevance.



Scheme 20 Asymmetric synthesis of spiro[chroman-3,3′-pyrazol] scaffolds bearing an all-carbon quaternary stereocenter *via* an oxa-Michael–Michael cascade reaction.

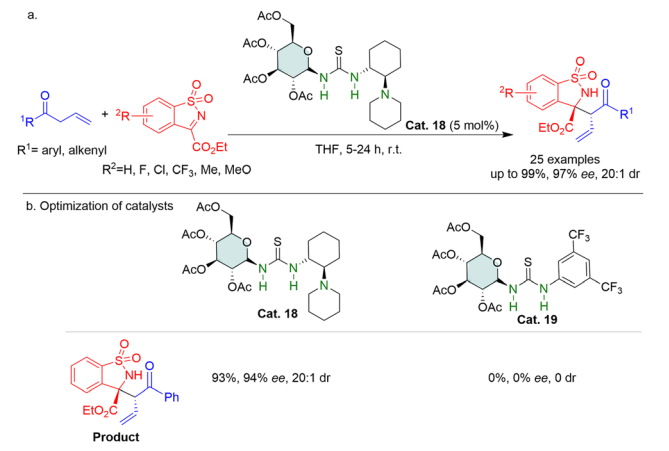
Mechanistically, in the proposed transition state I (TS I), (*E*)-2-(2-nitrovinyl)phenol is activated through dual hydrogen bonding between its nitro group and the thiourea moiety of the bifunctional catalyst **Cat. 15**. Simultaneously, the adjacent tertiary amine activates 4-benzylidene-5-methyl-2-phenylpyrazolone through enolate formation. The hydroxyl group of (*E*)-2-(2-nitrovinyl)phenol initiates the cascade by undergoing an intermolecular oxa-Michael addition to the pyrazolone *via* *Re*-face attack, yielding the intermediate transition state II (TS II). This is followed by an intramolecular Michael addition, also occurring on the *Re*-face, and the subsequent tautomerization furnishes the final spirocyclic product with the regeneration of the catalyst. The stereochemical outcome is largely dictated by the cooperative effect of the thiourea unit and the cyclohexyl backbone of the catalyst, which together govern both activation and stereoselectivity throughout the cascade. Yuan *et al.* reported the first hydrogen-bond-directed enantioselective decarboxylative Mannich reaction of β-ketoacids with ketimines, representing a significant advancement in organocatalytic asymmetric synthesis (Scheme 21a).[175] Their initial investigation focused on the reaction between 3-oxo-3-phenylpropanoic acid and a model ketimine substrate, catalyzed by a bifunctional thiourea–tertiary amine organocatalyst derived



Scheme 21 First example of hydrogen-bond-directed enantioselective decarboxylative Mannich reaction of β-ketoacids with ketimines. PMB = *para*-methoxybenzyl. Reproduced from ref. 175 with permission from John Wiley and Sons, copyright 2013.

from NCCs. Using the D-glucose-derived catalyst **Cat. 17** in THF at −20 °C for 48 hours, the desired Mannich product was obtained in 99% yield and 99% enantiomeric excess (ee, +). Remarkably, under identical conditions, the L-glucose-derived diastereomer **Cat. 16** afforded the same yield but with the opposite enantiomer in 96% ee (−), clearly demonstrating the enantiocontrol capability of the carbohydrate-derived scaffold. This methodology enabled the synthesis of a wide range of enantioenriched 3,4-dihydroquinazolin-2(1*H*)-one derivatives bearing a quaternary stereocenter with excellent yields (92–99%) and high enantioselectivities (90–99% ee). The utility of this approach was further exemplified in the asymmetric total synthesis of the anti-HIV drug DPC 083, highlighting its potential in drug discovery and development. Mechanistic studies, supported by computational analysis (Scheme 21b), revealed that the cyclic *N*-acyl ketimine is activated and precisely oriented by dual hydrogen bonding interactions with the thiourea moiety of **Cat. 17**. In addition, a stabilizing H–π interaction was identified between the aromatic protecting group on the ketimine substrate and the carbohydrate framework of **Cat. 17**. This interaction was shown to be critical for enantioselectivity, as substrates lacking an aromatic protecting group exhibited significantly diminished stereoselectivity. Furthermore, the tertiary amine unit of **Cat. 17** engages in electrostatic interactions with the β-ketoacid, facilitating nucleophilic activation. Collectively, these interactions promote a *Si*-face-selective nucleophilic addition to the C=N bond, ultimately leading to the formation of the *R*-enantiomer of the Mannich product upon decarboxylation. This work elegantly demonstrates how strategic hydrogen bonding and secondary interactions in organocatalysts can be harnessed to control complex stereoselective transformations.

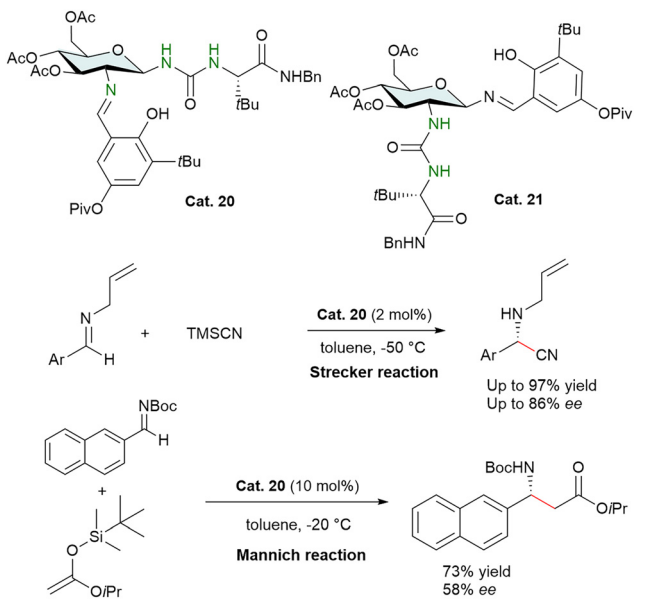
Qiao *et al.* developed an organocatalytic asymmetric Mannich reaction between allylic ketones and cyclic *N*-sulfonyl α-iminoesters, providing access to highly functionalized tetrasubstituted α-amino esters (Scheme 22).[174]



Scheme 22 Highly regio-, diastereo-, and enantioselective Mannich reaction of allylic ketones and cyclic ketimines: access to chiral benzosultam.

Utilizing a carbohydrate-derived chiral tertiary amine–thiourea catalyst, a broad range of substrates underwent smooth transformations to afford the desired products in high yields with excellent regio-, diastereo-, and enantioselectivities. This reaction shares mechanistic and catalytic similarities with the oxa-Michael–Michael cascade strategy shown in Scheme 21, as both employ bifunctional organocatalysts featuring a thiourea moiety and a chiral tertiary amine framework. To probe the role of the tertiary amine group in the catalytic system, the reaction was performed under the standard conditions using catalyst **Cat. 18**, which furnished the Mannich product in 93% yield, with 94% enantiomeric excess (ee) and a diastereomeric ratio (dr) of 20 : 1. In stark contrast, the use of **Cat. 19**, lacking the tertiary amine functionality, failed to deliver any product. These findings clearly demonstrate that the tertiary amine group plays a crucial role in the activation of the allylic ketone, likely by facilitating enolate formation and stabilizing the transition state *via* bifunctional activation. The study highlights the importance of precise catalyst design in achieving high levels of stereoselectivity in organocatalytic asymmetric Mannich reactions.

Inspired by bifunctional urea–Schiff base organocatalysts,[181,184] enantioselective Strecker and Mannich reactions catalyzed by glucosamine-derived urea–amine organocatalysts have been reported (Scheme 23).[173] In the Strecker reaction, catalyst **Cat. 20** delivered the desired product with excellent enantioselectivity (95% ee), whereas its diastereomer **Cat. 21** resulted in only 15% ee. These results clearly demonstrate that the carbohydrate moiety serves not merely as a rigid cyclohexane scaffold but plays a more active stereoelectronic role in catalysis. Specifically, the superior perform-



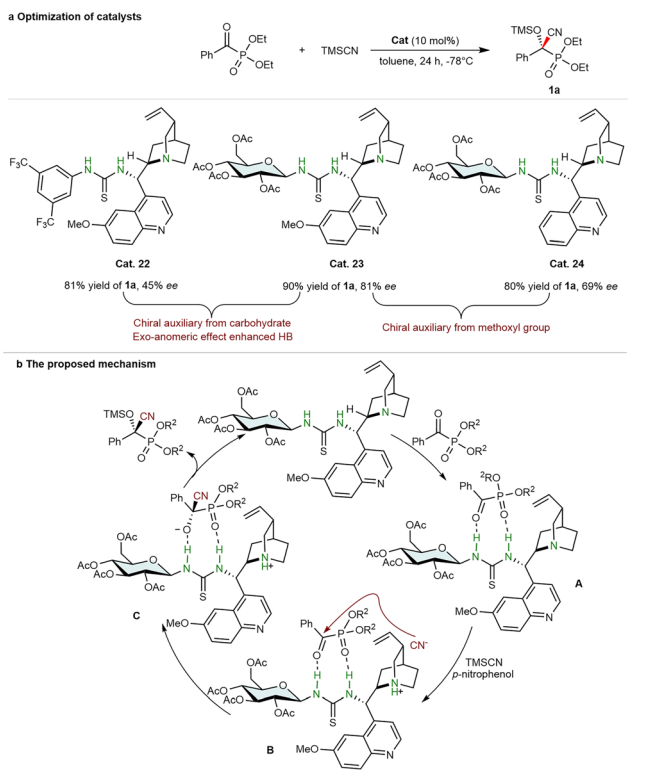
Scheme 23 Two bifunctional urea–Schiff base organocatalysts enantioselective for Strecker and Mannich reactions.

ance of **Cat. 20** can be attributed to the *exo*-anomeric effect, which influences the electronic environment at the anomeric position. This effect enhances the delocalization of *p*-electrons from the nitrogen substituent on the urea moiety, thereby increasing the NH-acidity of the urea. The result is a stronger hydrogen bond donating ability, which is crucial for substrate activation in both the Strecker and Mannich reactions. In contrast, **Cat. 21** exhibits a different configuration that diminishes the electron density at the imine nitrogen, reducing its effectiveness as a hydrogen bond acceptor. This weakened interaction compromises the stabilization of the phenolic OH group *via* hydrogen bonding, which is necessary for maintaining the conformational rigidity of the salen-type structure. Overall, this study underscores the critical role of stereoelectronic effects originating from the carbohydrate backbone in modulating catalyst performance and selectivity.

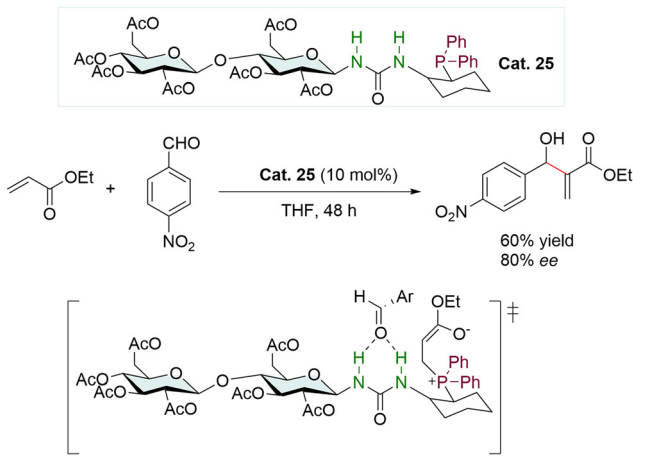
Kong *et al.* pioneered the development of a bifunctional sugar-derived thiourea–tertiary amine organocatalyst for the catalytic asymmetric addition of α-ketophosphonates to trimethylsilyl cyanide (TMSCN), achieving high yields and excellent enantioselectivities (Scheme 24).[110,168,176] Under standard conditions, catalyst **Cat. 22**, which lacks a carbohydrate moiety, afforded product **1a** in 81% yield but with only 45% enantiomeric excess (ee). In contrast, the sugar-derived **Cat. 23** delivered a significantly improved 81% ee with a 90% yield, highlighting the synergistic effect of incorporating both a cinchona alkaloid and a carbohydrate moiety within a single chiral organocatalyst. These findings confirm that the carbohydrate moiety plays an essential role as a chiral auxiliary and contributes stereoelectronic effects—most notably, the *exo*-anomeric effect, which enhances the hydrogen-bonding (HB) ability of the thiourea unit. Further comparison with **Cat. 24** demonstrated that the presence of a methoxy group, acting as a steric hindrance element, can also fine-tune the enantioselectivity of the reaction. Control experiments, including ^{31}P NMR monitoring under standard reaction conditions, supported the proposed mechanism. The thiourea moiety of the catalyst engages in hydrogen bonding with the α-ketophosphonate substrate, forming a stable intermediate (**A**). The *p*-nitrophenol additive is presumed to facilitate the *in situ* generation of hydrogen cyanide (HCN), the active nucleophile in the addition step. Nucleophilic attack by cyanide on the *Si* face of the α-ketophosphonate yields the *S*-configured enantiomer as the major product (**C**). In this process, the Re face is sterically shielded by the cinchona alkaloid scaffold, while the carbohydrate unit reinforces facial selectivity through its chiral auxiliary effect. This work elegantly illustrates how carefully designed bifunctional organocatalysts incorporating both sugar and alkaloid motifs can enable highly efficient and selective asymmetric transformations.

4.3. N-containing carbohydrate derived other type of organocatalyst

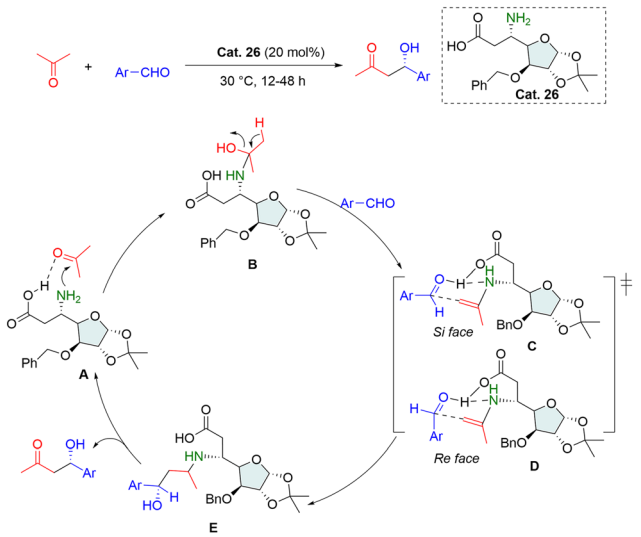
Porwański developed a series of chiral urea-based organocatalysts incorporating both glycosyl and diphenylphosphinyl scaffolds, synthesized *via* a one-pot tandem Staudinger/aza-Wittig coupling reaction (Scheme 25).[193] The novel catalyst **Cat. 25** was applied for the first time in the asymmetric Morita–Baylis–Hillman (MBH) reaction. Although the reaction proceeded with moderate yields, it delivered promising enantioselectivities, achieving up to 80% ee.



Scheme 24 Catalytic asymmetric addition of α-ketophosphonates to trimethylsilyl cyanide.



Scheme 25 Example of asymmetric Morita–Baylis–Hillman (MBH) reaction.



Scheme 26 Glycosyl-β-amino acids promote the enantioselective aldol reaction.

This work represents an important step in the design of multifunctional carbohydrate-derived organocatalysts and highlights the potential of combining glycosyl and phosphinyl frameworks to induce chirality in asymmetric transformations.

Dwivedi *et al.* developed an asymmetric organocatalytic method employing glycosyl-β-amino acids to promote the enantioselective aldol reaction of acetone with various aldehydes (Scheme 26).[178] Using 5-amino-5-deoxy-β-L-ido-(α-D-*gluco*)-heptofuranuronic acid (**Cat. 26**) as a novel class of organocatalyst, the reaction proceeded smoothly, affording the aldol products in good yields and with high enantioselectivities. This study highlights the potential of carbohydrate-derived β-amino acids as efficient and environmentally benign organocatalysts for stereoselective carbon–carbon bond formation. Wong *et al.* demonstrated that the sugar moiety of a glycopeptide, modified with a thiol handle at the C2 position, can facilitate the ligation of cysteine-free glycopeptides to peptide thioesters.[185–189] In this study, they proposed that the sugar moiety enhances the proximity between the N-terminal amine of the glycopeptide and the thioester functionality, thereby promoting acyl transfer and formation of the ligated product. However, the authors did not address the stereochemical configuration of the anomeric center or the nature of the N-linked sugars, nor did they explore how these factors might influence the efficiency or outcome of the ligation process. The same group expanded their approach to include more structurally elaborate sugars, broadening the scope of glycopeptide ligation strategies.[187] Building on this foundation, Liu *et al.* subsequently reported a practical method for synthesizing *N*-glycopeptides *via* an auxiliary-mediated dual native chemical ligation approach, providing a robust and versatile platform for the assembly of complex glycoprotein structures.[190]

5. Conclusions and perspectives

In recent years, NCCs, such as chitin, chitosan, glucosamine, and their derivatives, have emerged as highly promising, nitrogen-rich renewable feedstocks for the development of value-added chemicals, chiral ligands, and asymmetric catalysts. Their intrinsic structural features, including natural chirality, anomeric configurations, and dense hydrogen-bonding sites, offer compelling advantages in green and enantioselective synthesis, while providing a sustainable alternative to fossil-derived resources. This review has highlighted the role of NCCs as feedstocks, ligands, and organocatalysts in organic catalysis. However, the field is still in its early stages, and critical scientific challenges remain. Addressing these will not only deepen our mechanistic understanding but will also open entirely new avenues of research. Below, we outline several promising directions that could shape the next decade of innovation in carbohydrate-based synthesis and catalysis.

5.1. Novel catalytic strategies for regioselective bond cleavage in NCCs

Existing methods for transforming nitrogen-containing carbohydrates (NCCs) often suffer from poor selectivity toward the desired products, largely due to harsh reaction conditions that indiscriminately cleave multiple chemical bonds. The development of milder catalytic approaches, such as photocatalysis and electrocatalysis, with high regioselectivity offers a promising route to overcome these limitations. Furthermore, there is a compelling need for methodologies that can directly convert chitin, chitosan, or even raw biomass such as crustacean exoskeletons into value-added products. However, the efficiency of obtaining target molecules from chitin is significantly lower than from monomeric precursors like glucosamine, owing to its highly crystalline structure and extensive intra- and intermolecular hydrogen bonding. Future research should therefore focus on strategies to enhance chitin's accessibility and reactivity, for example by disrupting its crystalline domains and weakening hydrogen-bond networks, thereby enabling more efficient catalytic conversion under mild and selective conditions.

5.2. Merging NCCs with emerging catalysis platforms

The integration of NCC-derived chiral frameworks with photoredox catalysis and enzymatic catalysis systems offers fertile ground for discovering new asymmetric transformations. For example, combining carbohydrate-derived ligands/organocatalysts with light-driven or enzyme-mediated pathways may unlock stereoselective reactions that are inaccessible *via* traditional strategies. These hybrid approaches could significantly enhance both the reactivity and selectivity of complex molecule construction.

5.3. Mechanistic exploration of carbohydrate stereochemistry

Despite their widespread availability and structural diversity, the stereoelectronic effects and three-dimensional chiral environments of NCCs remain underexplored. Recent breakthroughs such as anomeric stereoauxiliary catalysis[82] and

glycan foldamers based on carbohydrate–aromatic interactions[191] have demonstrated new modes of asymmetric induction. A more detailed mechanistic understanding will enable the rational design of next generation carbohydrate-based catalysts, beyond empirical screening.

5.4. Rare sugar synthesis *via* site-selective epimerization

The site-selective photocatalytic epimerization of common sugars has recently emerged as a powerful tool to access rare sugar isomers.[192] These sugars greatly expand the chemical diversity of NCCs and serve as precursors for novel glyco-based therapeutics and catalysts. Continued exploration in this area is expected to produce high-value targets from low-cost biomass, accelerating drug discovery and molecular editing.

5.5. Reviving and redesigning NCC-based ligands

Although carbohydrate-derived ligands have a historical footprint in asymmetric metal catalysis, innovation in their design has slowed in recent years due to synthetic complexity and limited substrate scope. However, the development of modular ligand platforms, such as phosphite-oxazolines and C_2-symmetric bis(oxazoline) frameworks, offers a renewed opportunity. Future work should focus on designing ligands with tunable stereoelectronic properties, broader applicability, and compatibility with low-loading and scalable processes.

5.6. Catalytic glycosylation and site-selective chitosan modification

The recent paradigm shifts in glycosylation chemistry, where minimally protected donors and acceptors can undergo efficient catalytic coupling, has dramatically simplified carbohydrate functionalization.[193,194] In parallel, site-selective modification of chitosan is gaining momentum as a strategy for crafting functional biomaterials for tissue engineering, biosensing, and drug delivery.[26,195–197] These advances in organic synthesis reinforce the unique role of NCCs in bridging molecular synthesis and biomedical applications.

5.7. Chemical biology and protein degradation

The application of NCCs in chemical biology is expanding. A striking example is the development of LYTACs (lysosome-targeting chimeras) utilizing NCCs ligands (*e.g.*, GalNAc) to engage the asialoglycoprotein receptor (ASGPR) for cell-specific extracellular protein degradation.[198] This represents a powerful new interface between carbohydrate chemistry and precision medicine, and we expect this strategy to be extended to other carbohydrate-receptor systems in the near future.

The strategic valorization of NCCs represents a fundamental shift in synthetic chemistry, from a reliance on fossil feedstocks to the use of renewable, multifunctional molecular platforms. By linking organic catalysis, glycoscience, and materials engineering, NCCs offer a solution to challenges in sustainable chemical synthesis. We envision that cross-disciplinary efforts, spanning synthetic organic chemistry, enzymology, photochemistry, and polymer science, will be essential to fully unlock the potential of NCCs. The next decade is likely to witness transformative advances in carbohydrate-based catalysis and material design, positioning NCCs at the center of green, asymmetric, and precision-oriented molecular science.

Author contributions

K. Z. conceived the concept and wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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