Anomeric Stereoauxiliary Cleavage of the C—N Bond of D-Glucosamine for the Preparation of Imidazo[1,5-a]pyridines

Kui Zeng,[a] Jin Ye,[b] Xintong Meng,[a] Sebastian Dechert,[c] Martin Simon,[d] Shuaiyu Gong,[a] Ricardo A. Mata,[b] and Kai Zhang*[a]

Abstract: The targeted cleavage of the C—N bonds of alkyl primary amines in sustainable compounds of biomass according to a metal-free pathway and the conjunction of nitrogen in the synthesis of imidazo[1,5-a]pyridines are still highly challenging. Despite tremendous progress in the synthesis of imidazo[1,5-a]pyridines over the past decade, many of them can still not be efficiently prepared. Herein, we report an anomeric stereoauxiliary approach for the synthesis of a wide range of imidazo[1,5-a]pyridines after cleaving the C—N bond of D-glucosamine (α-2° amine) from biobased resources. This new approach expands the scope of readily accessible imidazo[1,5-a]pyridines relative to existing state-of-the-art methods. A key strategic advantage of this approach is that the α-anomer of D-glucosamine enables C—N bond cleavage via a seven-membered ring transition state. By using this novel method, a series of imidazo[1,5-a]pyridine derivatives (>80 examples) was synthesized from pyridine ketones (including *para*-dipyridine ketone) and aldehydes (including *para*-dialdehyde). Imidazo[1,5-a]pyridine derivatives containing diverse important deuterated $C(sp^2)$—H and $C(sp^3)$—H bonds were also efficiently achieved.

Introduction

C—N bonds are ubiquitous in many biobased organic molecules, especially in the many biomolecules of living organisms.[1] The utilization and transformation of C—N bonds are among the central topics in organic chemistry, biochemistry and material science,[2] although only a few examples of the C—N cleavage of alkyl primary amines have been reported recently with the assistance of metal-catalysts. Up to now, most protocols have been limited to primary amines with benzylic, allylic and pyridine.[2d,3] It is still highly attractive to develop efficient strategies for selective C—N bond cleavage in alkyl primary amines, including α-1°, α-2° and α-3° alkyl primary amines. In 2017, the Watson group cleaved C—N bonds of α-1° and α-2° primary alkyl amines by single electron transfer to Katritzky pyridinium salt intermediates (Scheme 1a).[4] Later in 2020, the Rovis group demonstrated a visible-light photoredox approach to cleaving the C—N bonds of α-3° primary alkyl amines via a key imidoyl radical intermediate (Scheme 1a).[5] Moreover, the Milstein group reported a catalytic oxidative deamination

[a] K. Zeng, X. Meng, S. Gong, Prof. Dr. K. Zhang
Sustainable Materials and Chemistry
Georg-August-University of Göttingen
Büsgenweg 4, 37077 Göttingen (Germany)
E-mail: kai.zhang@uni-goettingen.de

[b] J. Ye, Prof. Dr. R. A. Mata
Institute of Physical Chemistry
Georg-August-University of Göttingen
Tammannstraße 6, 37077 Göttingen (Germany)

[c] Dr. S. Dechert
Institute of Inorganic Chemistry
Georg-August-University of Göttingen
Tammannstraße 4, 37077 Göttingen (Germany)

[d] M. Simon
Institute of Organic and Biomolecular Chemistry
Georg-August-University of Göttingen
Tammannstraße 2, 37077 Göttingen (Germany)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202200648
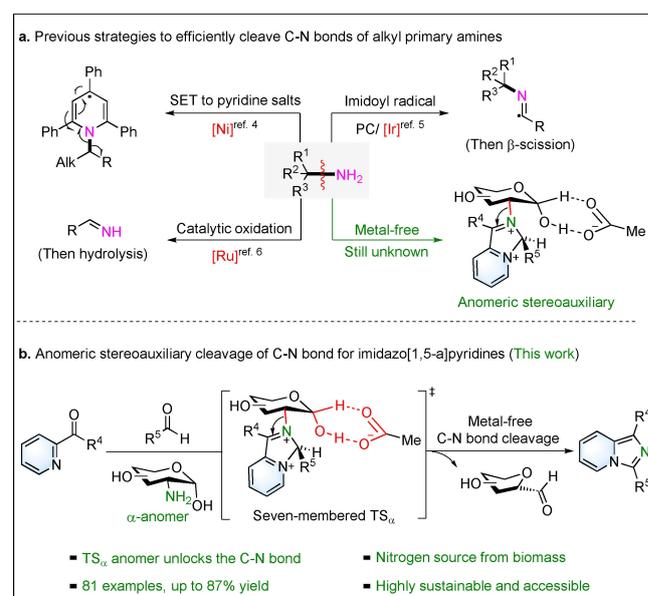
Scheme 1. a) Representative examples of previous strategies for the cleavage of the C—N bonds of alkyl primary amines. b) Our strategy: cleavage of the C—N bond of imidazo[1,5-a]pyridines via an anomeric stereoauxiliary.

Chem. Eur. J. **2022**, *28*, e202200648 (1 of 9)

© 2022 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

Chemistry
Europe
European Chemical
Societies Publishing

protocol with a ruthenium pincer complex (Scheme 1a).[6] Until now, all the reported methods for C–N bond cleavage in alkyl primary amines required transition metal catalysts. Unlike these previous strategies towards the cleavage of C–N bond by metal catalysts, the metal-free anomeric stereoauxiliary strategy to cleave the C–N bond of native D-glucosamine (α-2° amine) from biobased resources we present here offers a readily accessible and sustainable route for the synthesis of a broad range of imidazo[1,5-a]pyridines (Scheme 1b).

Imidazo[1,5-a]pyridines, as one of the most important N-heterocyclic compounds, play pivotal roles in various areas from pharmaceutics over chemical synthesis to materials science.[7] For example, they can be precursors of N-heterocyclic carbenes,[7a–c] ligands in coordination chemistry,[7d,e] and inhibitors of biologically active agents.[7f–h] In particular, due to the unique photophysical properties with quantum yields up to 50%, large Stokes shift (up to 100–150 nm) and good stability,[8] imidazo[1,5-a]pyridines are attractive optical materials for many applications.[9] In this respect, advances from metal-free to metal-catalyzed cyclization strategies of N-heterocyclic substrates have increased the number of accessible structures. A representative metal-free method with NH_4OAc as nitrogen source for imidazo[1,5-a]pyridines was reported in 2005.[10] This method was continually improved and widely used in synthetic chemistry and for optical materials,[11] even though the challenges still need to be addressed. For instance, many imidazo[1,5-a]pyridines including 1-alkylimidazo[1,5-a]pyridines and 3-alkylimidazo[1,5-a]pyridines are inaccessible by this method.
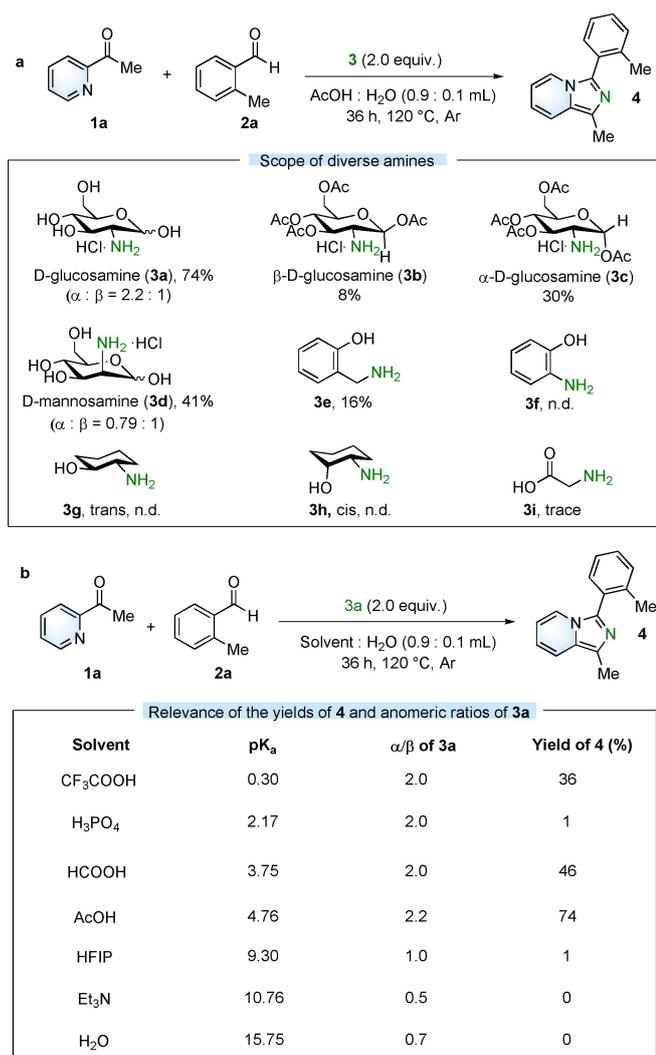
In 2007, Gevorgyan reported the first efficient rhodium-catalyzed metal carbine approach for the preparation of imidazo[1,5-a]pyridines by transannulation of pyridotriazoles process.[12] 3-alkylimidazo[1,5-a]pyridine products (6 examples) were unprecedentedly accessed with this metal-catalyzed method. It was shown that an activating group (Cl, Br, or OMe substituents) at C_7, as well as electron-withdrawing groups at C_3, were necessary for an efficient formation of imidazo[1,5-a]pyridines. To overcome these limitations, a general strategy of rhodium-catalyzed NH insertion of pyridyl carbenes for imidazo[1,5-a]pyridines was developed in 2014.[13] Although this strategy widely expanded the library of accessible structures, the study showed only six examples in total and the required precious metal catalyst with active triazole substrates hinders its widespread applications. In 2014 and 2016, inexpensive copper catalysts were applied for synthesizing imidazo[1,5-a]pyridines, but these methods are limited to 3-monosubstituted imidazo[1,5-a]pyridines, while many imidazo[1,5-a]pyridines maintain inaccessible, such as 1-alkylimidazo[1,5-a]pyridines.[14b] The challenges in accessing 1-alkylimidazo[1,5-a]pyridines by ketone activation of alkyl(pyridine-2-yl)methanone substrates lies in the lower reactivity of alkyl(pyridine-2-yl)methanone compared to aryl(pyridin-2-yl)methanone.[14a] Additionally, alkyl(pyridine-2-yl)methanone is readily activated as nucleophilic reagent due to the α-saturated C–H bond next to ketone, which can result in a side reaction.[15] Therefore, it is highly desired to develop a strategy to overcome these disadvantages.

Carbohydrates as chiral auxiliaries in stereoselective synthesis[16] and stereochemistry of transition metal complexes controlled by the metallo-anomeric effect[17] have drawn much attention recently. Depending on the pK_a values of aqueous solutions, the α/β-anomers of D-glucosamine exist with adjustable ratios.[18] Inspired by these different stereochemical structures of α/β-anomers, we demonstrate herein a novel strategy for the cleavage of C–N bond in D-glucosamine that is enabled by α-anomer through the formation of a key (non-covalent) seven-membered ring transition state for the synthesis of diverse imidazo[1,5-a]pyridines without any metal catalysts. Various inaccessible substrates from existing methods for imidazo[1,5-a]pyridines are synthetically accessible by this protocol.

Results and Discussion

We commenced our study by probing various reaction conditions for imidazo[1,5-a]pyridines by using 2-acetylpyridine (**1a**), 2-methylbenzaldehyde (**2a**) and diverse nitrogen sources (Table S1 in the Supporting Information). After extensive experimentation, we got the optimal conditions for the efficient synthesis of imidazo[1,5-a]pyridines with 74% yield by using D-glucosamine as nitrogen source in a solvent mixture ($v_{AcOH}:v_{H_2O}$ of 9:1) at 120°C under argon (Scheme 2a). In parallel, commercial acetylated amine sugars as stabilized α-anomer (**3b**) and β-anomer (**3c**) were used for the reaction under the optimal conditions (Scheme 2a). The α-anomer of acetylated D-glucosamine led to 30% yield, while only trace of the product was detected using the β-anomer. Therefore, the α-anomer of D-glucosamine with the hydroxy group at the neighbor C1 position is preferred for the synthesis of imidazo[1,5-a]pyridines. Besides, the scope with D-mannosamine under the same conditions led to a yield of 41% in the presence of a major β-anomer distribution (α/β = 0.79:1). This result further verified that the configuration of amine and hydroxy group should be on the same side to cooperatively cleave C–N bonds for imidazo[1,5-a]pyridines. Various amines (**3e** to **3i**) were also investigated. As a result, only **3e** fulfilling these configuration requirements provided the desired product with the highest yield of 16%.

To explore the correlation between the yield of imidazo[1,5-a]pyridine **4** and the anomer of D-glucosamine in solvents with diverse pK_a, solvent mixtures with various pK_a (0.9 mL) and H_2O (0.1 mL) were investigated under optimal conditions (Scheme 2b). In general, the ratio between α- and β-anomer of D-glucosamine (refers as α/β) highly depends on the pK_a of the respective solvent. Solvents with higher pK_a, such as HFIP (pK_a: 9.30), Et_3N (pK_a: 10.76) and H_2O (pK_a: 15.75), result in lower α/β ratios of glucosamine and significantly lower yields of imidazo[1,5-a]pyridine **4**. The predominant reason for this result should be the presence of the β-anomer of D-glucosamine as the major isomer. In comparison, those suitable acidic reaction media, such as CF_3COOH (pK_a: 0.30), HCOOH (pK_a: 3.75) and AcOH (pK_a: 4.76), result in higher α/β ratios of glucosamine and higher yields of **4**, showing the facilitating effect of the α-

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

Chemistry Europe
European Chemical
Societies Publishing

Scheme 2. Reaction development. a) Diverse amino compounds 3a–3i were used in reactions in the solvent mixtures (v_{AcOH}/v_{H_2O} 9:1) at 120 °C under argon. b) Various mixtures of solvents with diverse pK_a (0.9 mL) and H$_2$O (0.1 mL) were used for the reactions under optimal conditions. The pK_a values of CF$_3$COOH,[19] H$_3$PO$_4$,[20] HCOOH,[21] CH$_3$COOH,[22] 1,1,1,3,3,3-hexafluor-opropan-2-ol (HFIP),[23] Et$_3$N,[24] and H$_2$O[25] were determined at 25 °C. The ratios of α- and β-anomers were measured by ^{1}H NMR analysis at room temperature; Yields were determined by ^{1}H NMR analysis with CH$_2$Br$_2$ as the internal standard.

anomer of D-glucosamine on the synthesis of **4**. These results further indicate that Brønsted acids with suitable pK_a stabilize the methyl group of alkyl(pyridine-2-yl)methanone, and thus hinder the deprotonation of the methyl group.[26]
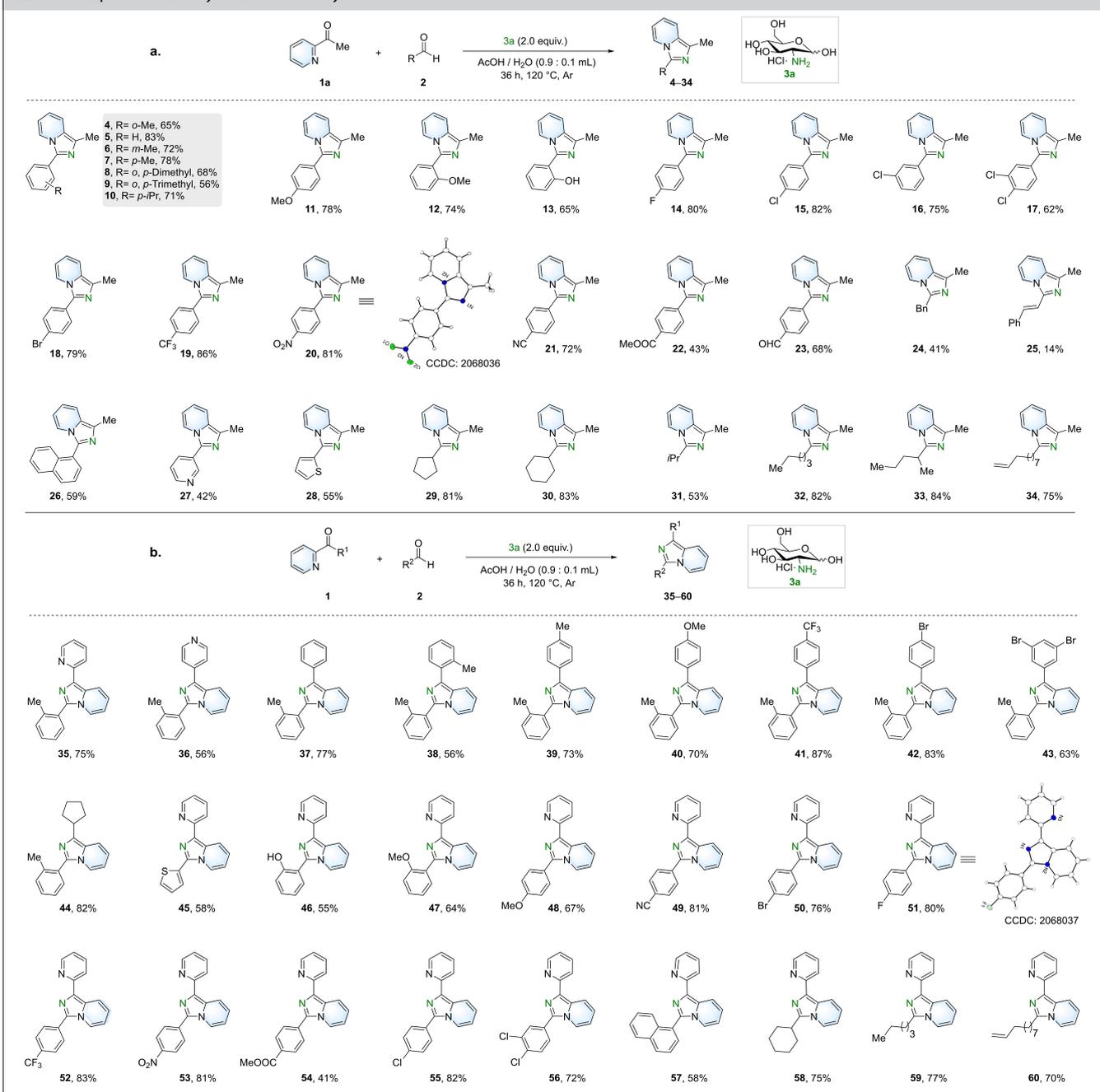
With the optimized reaction conditions in hand, we next probed the scope of various aldehydes using 2-acetypyridine as a representative heteroaryl ketone (Table 1a). An array of aromatic aldehydes, including those with electron-donating or -withdrawing groups at different positions (*ortho*, *meta* or *para*), were efficiently transformed to the corresponding products **4**–**23**. A variety of valuable functional groups at diverse positions, such as methoxy (**11** and **12**), halogens (**14**–**18**), trifluoromethyl (**19**), nitro (**20**), nitrile (**21**) and ester (**22**), were well compatible

with these conditions. Particularly, free *para*-dialdehyde (**23**) and *ortho*-phenolic hydroxyl (**13**) were also tolerated in this protocol. The structure of **20** was further confirmed by X-ray crystallographic analysis, and those of other products in Table 1 were assigned by analogy. Moreover, 2-phenylacetaldehyde (product **24**), cinnamaldehyde (product **25**), 1-naphthaldehyde (product **26**) and heterocyclic aldehydes (products **27** and **28**) were also well compatible with this approach. Furthermore, a series of aliphatic aldehydes, including cyclic aldehydes (prod-ucts **29**–**30**) and aldehydes with aliphatic chains (products **31**–**34**), could also be transformed into desired products. Hence, this facile and efficient approach has been proved for the successful preparation of saturated 1-alkylimidazo[1,5-a]pyridine compounds, with unprecedented use of inexpensive and commercially available aromatic/aliphatic aldehydes.

We further explored heteroaryl ketones (Table 1b). Di-(pyridin-2-yl)methanone (product **35**) and pyridin-2-yl(pyridin-4-yl)methanone (product **36**) were tolerated in this reaction. Various aromatic pyridine ketones, including those having electron-donating or -withdrawing groups at distinct positions (*ortho*, *meta* or *para*), were well transformed into the corre-sponding products **37**–**43**. The functional groups at diverse positions, such as methyl (**38** and **39**), methoxy (**40**), trifluoromethyl (**41**), mono-Br- (**42**) and di-Br-substituted arenes (**43**), were fully compatible with our conditions. The cyclic aliphatic pyridine ketone was also tolerated under these conditions (**44**). In addition, our protocol was also capable for the assembly of diverse tridentate (**45**–**47**), bidentate ligands (**48**–**60**), and heterocyclic backbones with fluorescent proper-ties. The structure of **51** was further assigned with X-ray crystallographic analysis.

Certain imidazo[1,5-a]pyridines with multiple substitutions show interesting optical properties and ligand effects due to the conjugation feasibility and the presence of lone pair electrons in nitrogen and oxygen atoms. Because of the difficulty for the regioselective functionalization and the interference of potential side reactions, there is still no efficient method to synthesize such compounds so far. With our method, the challenging bifunctionalization of dialdehyde (product **61**) was achieved smoothly (Scheme 3a). Motivated by this result, 1,4-phenylenebis(pyridin-2-ylmethanone) (product **62**) was also prepared according to our synthetic route (Scheme 3b). In addition, starting from **50**, products **63** and **64** were readily obtained with yields of 68% and 72% after the reaction with diphenylphosphine oxide and phenylboronic acid, respectively (Scheme 3c and d). Moreover, imidazo[1,2-a:3,4-a′]dipyridin-10-ium (**65**) was accessed concisely after two steps with standard conditions (Scheme 3e).

Isotope labeling, such as deuterated fine chemicals, has a broad range of applications, for instance for drug absorption, distribution, metabolism and excretion, for the investigation of reaction processes and for imaging.[27] The first deuterated drug, deutetrabenazine, was approved by FDA in 2017.[28] Because of the versatile functionalities of imidazo[1,5-a]pyridines that are interesting for diverse fields ranging from material science to pharmaceutics, efficient synthetic methods for deuterated

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

Chemistry Europe
European Chemical
Societies Publishing

Table 1. Scope of the aldehydes and heteroaryl ketones.[a]

[a] Reactions were carried out at 120 °C with heteroaryl ketones, aldehyde, D-glucosamine·HCl (**3 a**) in AcOH/H₂O (0.9:0.1 mL), under argon with stirring for 36 h. Yields are those of the isolated products.
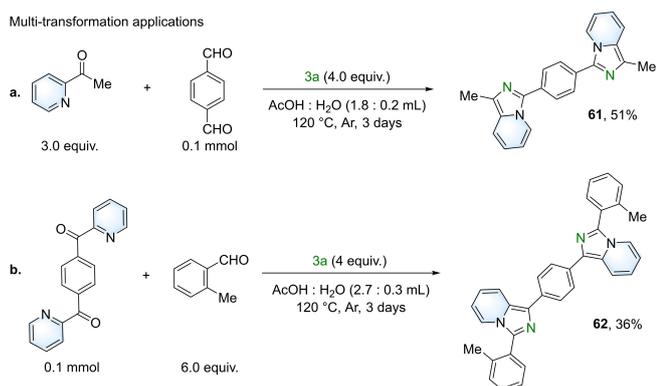
building blocks of imidazo[1,5-a]pyridines derivatives are highly desired.

The protons at the α-position of pyridine ketone and aliphatic aldehydes could reversibly exchange with acidic aqueous surroundings (Figures S18 and S19). With our protocol, deuterated imidazo[1,5-a]pyridines were readily synthesized in a one-pot process with the simultaneous cleavage of the C–N bond of D-glucosamine. The aromatic aldehydes with electro-withdrawing and electro-donating groups at diverse positions were transformed into deuterated products with high yields
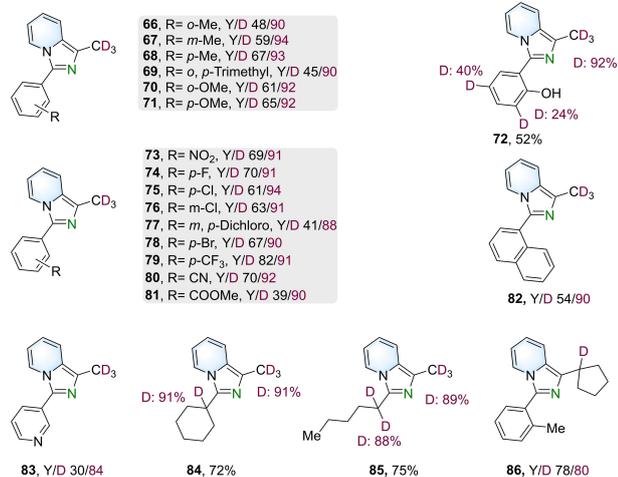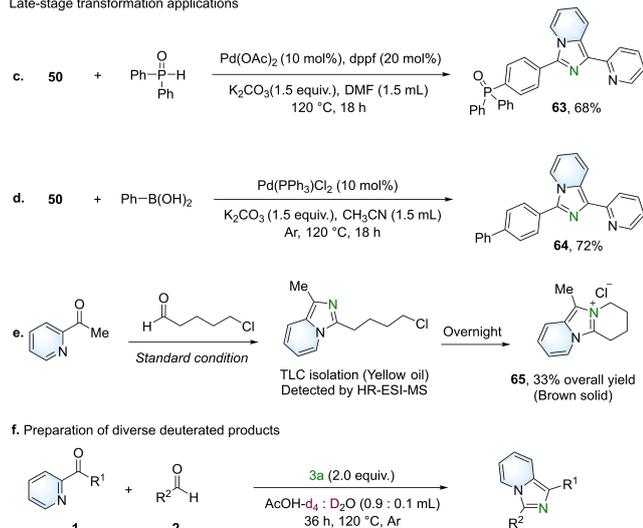
(**66–81**; Scheme 3f). Moreover, 1-naphthaldehyde, pyridine aldehyde and cyclopentyl(pyridin-2-yl)methanone were also compatible with the reaction condition (products **82**, **83** and **86**). In addition, the products **84** and **85** even achieved the efficient deuteration at multiple positions.

Process mass intensity (PMI) is a key mass-based metric to evaluate the green credentials of reactions during process and chemical development.[29] The calculations of the PMI for our current work as well as for representative approaches are shown comparatively[10,13,14] (Table 2). The PMI$_{RRC}$ (expressed as

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

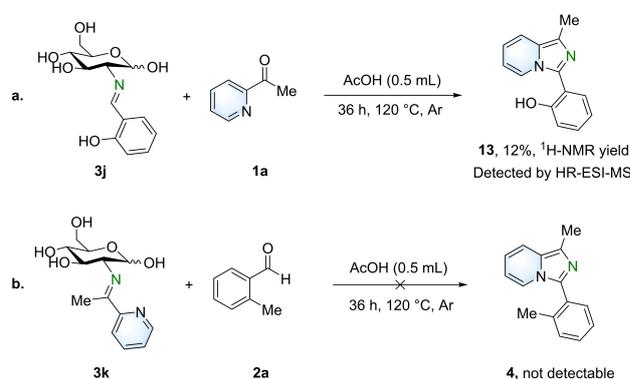**Chemistry Europe**
European Chemical
Societies Publishing

Scheme 3. Synthetic applications. All yields are isolated products, and the D incorporation in Scheme 4g was measured by ¹H NMR analysis.

the amount of reagents, reactants and catalyst) of our strategy is slightly higher than the previous presentative approaches, while the PMI$_{Solv}$ (solvent relative to the amount of isolated product) of the approach from Gevorgyan's group[13] is higher than ours and the other two approaches.[10,14] It should be noted that PMI$_{Solv}$ does not take into account of any solvent consumed
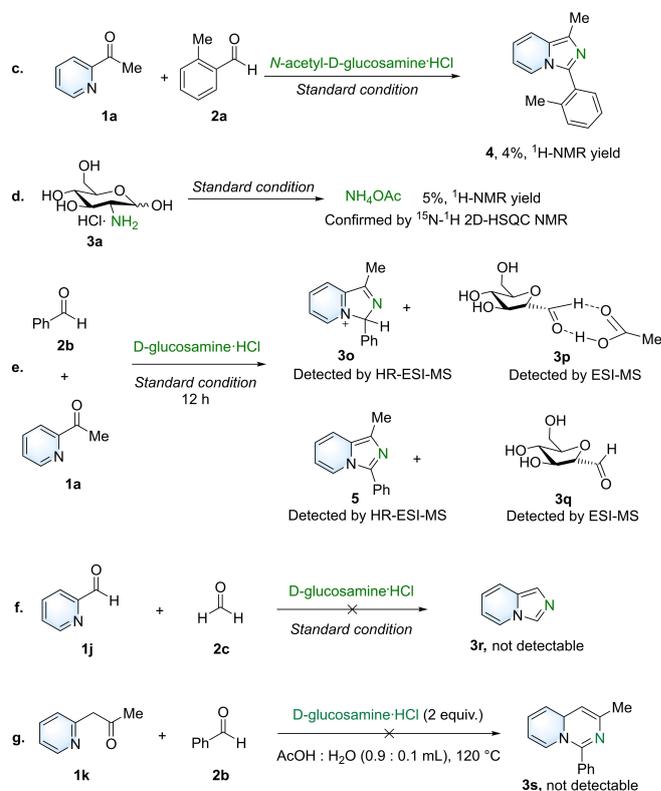
during purification processes since the reference values for the comparative works are not available.

To gain insight into the mechanism, a set of control experiments were conducted (Schemes 4 and 5, below). D-glucosamine is able to form imines and azomethines with aldehydes and ketones[30] and the hydroxy groups of D-glucosamine can be modified by substitution reactions.[31] In the first group of control experiment, intermediates **3j** and **3k** were used to verify the reaction order (Scheme 4a and b).[30,32] As a result, product **13** was detected by ¹H NMR spectroscopy and further confirmed by HR-ESI-MS (Scheme 4a), while product **4** was not detectable (Scheme 4b). We therefore suggest that D-glucosamine reacted with aldehyde at first to form the imine intermediate.
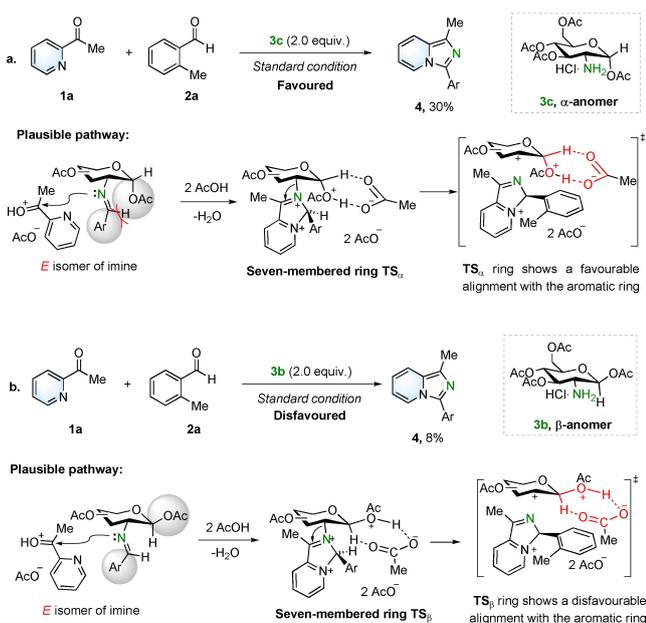

Scheme 4. Reaction pathway control experiments.

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

Chemistry Europe
European Chemical
Societies Publishing

Table 2. The calculations of process mass intensity.

Ref.	Representative approaches		Yield	PMI$_{RRC}$ g·g^{-1}	PMI$_{Solv}$ g·g^{-1}	PMI g·g^{-1}
10			81%	3.6	47.8	51.4
13			73%	3.4	87.0	90.4
14a			93%	3.8	0.7	4.5
This work			83%	4.4	60.5	64.9

Scheme 5. Anomeric stereoauxiliary control experiments.

In the second group of control experiment, *N*-acetyl-ᴅ-glucosamine was examined under standard conditions (Scheme 4c). The results rule out the cleavage pathway by N-acetylation of ᴅ-glucosamine. In the absence of aldehyde and 2-acetylpyridine, only traces of ammonium acetate were detected by ^{1}H NMR (Scheme 4d). The ammonium acetate was further verified by two-dimensional ^{1}H,^{15}N heteronuclear single quantum coherence (HSQC) NMR measurement (Figures S10 and S11), which excluded the pathway of thermo-cleavage of

the C–N bond in ᴅ-glucosamine. Moreover, the intermediates **3o**, **3p**, **3q** and **5** were detected by HR-ESI-MS and ESI-MS, which reveal the late-stage pathway with the formation of derivatives of imidazo[1,5-a]pyridines and furanoses as the intermediates after the cleavage of the C–N bond of ᴅ-glucosamine (Scheme 4e). The isolation of furanoses is rather difficult due to the unstable properties under the acidic conditions at high temperature (Figure S25). A group of molecules can be detected (99, 131, and 159 g/mol, etc.). This indicates that the furanose is not stable and it might degrade into smaller molecules. Even though furanose has been obtained as by-product from ᴅ-glucosamine in this approach, furanose with a pending aldehyde group and hydroxy groups represents an interesting starting material for platform chemicals including synthesis of furanose sugars,[33] nucleophilic substitution at the anomeric position of furanose,[34] equilibrium and non-equilibrium furanose selection in the ribose isomerization network[35] and synthesis of furanose-based carbohydrates.[36]

Furthermore, picolinaldehyde (**1j**) and formaldehyde (**2c**) were used for the same protocol under standard conditions, which excluded the pathway of post dealkylation of imidazo[1,5-a]pyridinium salts (Scheme 4f).[37] 1-(pyridin-2-yl)propan-2-one (**1k**) reacts with benzaldehyde (**2b**) under the same conditions. In contrast, the N-transfer process from glucosamine to the N-heterocyclic chemical (**3s**) failed (Scheme 4g).

In further control groups, 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-ᴅ-glucopyranose hydrochloride (**3b**) and 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-ᴅ-glucopyranose hydrochloride (**3c**) were tested under the same conditions (Group 3 in Scheme 4a and b). **3b** and **3c** show stable and pure β-anomer and α-anomer structures, respectively, while the anomer of ᴅ-

Chem. Eur. J. **2022**, *28*, e202200648 (6 of 9)

© 2022 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH

Chemistry–A European Journal

Research Article
doi.org/10.1002/chem.202200648

Chemistry Europe
European Chemical
Societies Publishing
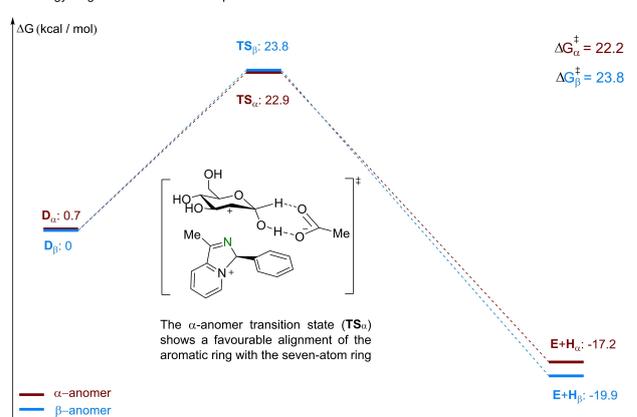
glucosamine is unstable. Therefore, **3b** and **3c** can be used to verify whether the α/β-anomer can affect the yield of product **4**. As a result, product **4** with 30% yield was obtained using **3c** (α-anomer), while **3b** (β-anomer) could only deliver 8% yield. Based on the results shown in Scheme 4, plausible reaction pathways for TS$_\alpha$ and TS$_\beta$ are proposed in Scheme 5 to explain the distinct reaction activities between **3c** (α-anomer) and **3b** (β-anomer). First, in comparison to **3b** (β-anomer), **3c** (α-anomer) should favor the formation of the *E* isomer of imine due to the steric hinderance (Scheme 5a). Moreover, the α-anomer promotes the formation of a seven-membered ring transition state with the acetate anion in solutions through hydrogen bonds. This ring of the α-anomer transition state (TS$_\alpha$) not only helps to stabilize the intermediate during the cleavage of the C−N bond, but also shows a favorable alignment with the aromatic ring. **3b** (β-anomer) forms a seven-membered ring transition state with β-anomer through a hydrogen bond between the acetyl group of the β-anomer and the acetate anion (Scheme 5b). The *E* isomer of imine forms more easily,[30] and the stronger steric shielding from seven-membered ring transition state also contributes to the formation. The ring of the β-anomer transition state (TS$_\beta$) shows an unfavorable alignment with the aromatic ring. The energy states of both TS$_\alpha$ and TS$_\beta$ via D-glucosamine were calculated by electronic structure calculations (Scheme 6b). Hence, based on the results shown in Schemes 2, 4 and 5, a seven-membered ring of α-anomer transition state (TS$_\alpha$) formed through hydrogen bonds, which favors the following cleavage of C−N bond.[38] Combining all results, a plausible mechanism is proposed (Scheme 6a).

First, D-glucosamine reacts with aldehyde to form imine **A**. Then, **A** attacks the ketone of pyridine ketone through nuleophilic addition to generate the intermediate **B**.[39] Under acidic conditions with acetic acid, a seven-membered ring of α-anomer transition state (TSα) forms. The nitrogen of pyridine attacks the imine by nucleophilic addition to form the intermediate **C**. Under acidic conditions, the intermediate **D** forms through dehydration. The seven-membered ring of α-anomer transition state (TS$_\alpha$) helps to stabilize the transition state when the C−N bond of the intermediate **D** is cleaved. The cleavage of the C−N bond in **D** results in intermediates **E** and **F**. Intermediate **F** shows a favorable alignment with the seven-membered ring. Due to the unstable transition state of **F**, **H** forms rapidly after the ring opening of **F** and further leads to **I**. In parallel, the deprotonation of **E** results in the product **G**.

Based on the proposed mechanism and control experiments, theoretical calculations were performed for the reaction step of the C−N bond cleavage (**D**→**E**+**H**) with the consideration of the stereoselectivity to further support the proposed mechanism. The calculated final Gibbs free energy of the transition state of the α-anomer (**TS$_\alpha$** in Scheme 6b) was 0.9 kcal/mol, which is lower than that of the β-anomer (**TS$_\beta$**). Since the Gibbs free energy of the reactant connected to **TS$_\alpha$** (**D$_\alpha$**) was 0.7 kcal/mol higher than that connected to **TS$_\beta$** (**D$_\beta$**), the reaction barrier for the α-anomer is thus 1.6 kcal/mol and lower than that of the β-anomer (22.2 vs. 23.8 kcal/mol). Given that the two anomers do not stand in kinetic competition (they are utilized in separate reactions), the latter value should be

a. Proposed mechanism.
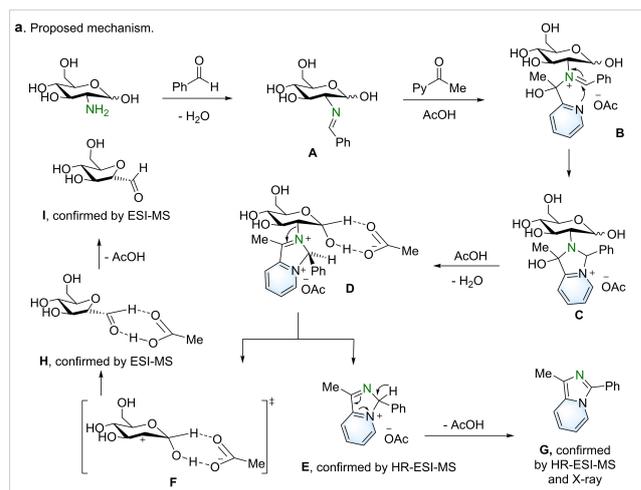
b. Energy diagram for the reaction step D ⟶ E+H

$\Delta G^\ddagger_\alpha = 22.2$
$\Delta G^\ddagger_\beta = 23.8$

TS$_\beta$: 23.8
TS$_\alpha$: 22.9

D$_\alpha$: 0.7
D$_\beta$: 0

E+H$_\alpha$: -17.2
E+H$_\beta$: -19.9

The α-anomer transition state (**TS$_\alpha$**) shows a favourable alignment of the aromatic ring with the seven-atom ring

— α−anomer
— β−anomer

c. Simplified scheme of the computed DFT conformers for the mixture of D-glucosamine and HCl, discriminated according to the respective anomers. The relative energies (in kcal/mol) in respect to the most stable conformer are provided.

α
0.0   3.9   1.0

β
2.2   2.2   1.0
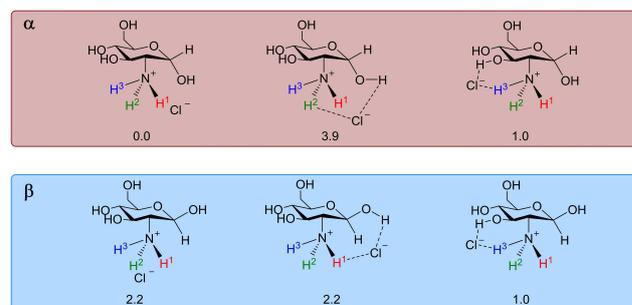
Scheme 6. a) Proposed mechanism and b), c) density functional theory calculation. Conformers in c are v1, v2 and v3 from left to right.

taken as the actual barrier difference. The acetate molecule stabilizes the transition state through the hydrogen bond as depicted in Scheme 5a, which is ultimately transferred. The ring system, as schematically shown in Scheme 5b, aligns with the carboxylic group through dispersion forces that could reduce the barrier. This stands as a further example for the importance of London forces in stereoselectivity.[40]

The α/β-ratio for the mixture of D-glucosamine and HCl was determined using the same theoretical method. Three conformers (Scheme 6c) were taken into consideration for each anomer, where the chloride might interact with each of the hydrogen atom of the protonated amine group. The Gibbs free energy of the α-v1 conformer was taken as reference for all the energy terms listed in Scheme 6c. For each anomer the Gibbs free energy was obtained by averaging the Gibbs free energies of the three conformers with their Boltzmann-factors and applying conformational entropy corrections. The resulting final Gibbs free energy was −0.1 kcal/mol for the α-anomer and 0.8 kcal/mol for the β-anomer, respectively. The energy difference of 0.9 kcal/mol corresponds to an α/β-ratio of 3.1 at the reaction temperature of 393.15 K. This difference would be reduced to 0.55 kcal/mol if one excludes the chloride anion. Such energy difference corresponding to an α/β-ratio of 2.0 gives us a range, which comfortably accommodates the experimental observations.

Conclusion

In summary, we have developed a novel α-anomeric stereoauxiliary strategy for the facile preparation of a broad range of imidazo[1,5-a]pyridines that features the cleavage of the C–N bonds of D-glucosamine via a seven-membered-ring transition state intermediate and the simultaneous incorporation of amine moieties into valuable imidazo[1,5-a]pyridines. This method unlocks efficient access to diverse imidazo[1,5-a]pyridine derivatives bearing sensitive functional groups that are inaccessible with conventional approaches. Various control experiments and DFT calculations revealed that the hydroxy group of the α-anomer promoted the formation of a seven-membered-ring transition state with the acetate anion through hydrogen bonding. The ring structure in the α-anomer transition state (TS$_\alpha$) not only helped to stabilize the intermediate during the C–N bond cleavage, but also profited from the dispersion interactions brought by the neighboring aromatic ring. Given the importance of imidazo[1,5-a]pyridines and C–N bond cleavage of aliphatic amine, we believe that this approach with combined anomer-assisting C–N bond cleavage by using native stereochemistry of D-glucosamine and the synthesis of imidazo[1,5-a]pyridines will be of significant and general interest for many fields, and open a new window for chemical synthesis.

Experimental Section

Preparation of imidazol[1,5-a]pyridines: A mixture of pyridine ketone, aldehyde and D-glucosamine·HCl in AcOH/H₂O was stirred at 120°C under argon for 36 h. The reaction was conducted in a sealed Schlenk flask and heated by an IKA magnetic heating agitator with oil bath. The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by thermometer. After cooling to room temperature, the reaction mixture was concentrated with rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl

acetate/n-hexane/Et₃N) to give products **4–62**. The deuterated products **66–86** were synthesized through an analogous procedure to method B using [D₄]AcOH/D₂O (0.9:0.1 mL) as solvent. More experimental details and characterization are available in the Supporting Information.

Deposition Numbers 2068036 (for **20**), 2068037 (for **51**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

[1] a) D. E. Canfield, A. N. Glazer, P. G. Falkowski, *Science* **2010**, *330*, 192–196; b) P. G. Falkowski, *Nature* **1997**, *387*, 272–275; c) *Enriching the Earth: Fritz Haber, Carl Bosch, and the Transformation of World Food Production* (Ed.: V. Smil), MIT Press, Cambridge, MA, **2004**, pp. 161–164.

[2] a) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852–860; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651–3678; d) K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev.* **2015**, *115*, 12045–12090.

[3] a) X.-S. Wu, Y. Chen, M.-B. Li, M.-G. Zhou, S.-K. Tian, *J. Am. Chem. Soc.* **2012**, *134*, 14694–14697; b) M. B. Li, Y. Wang, S. K. Tian, *Angew. Chem. Int. Ed.* **2012**, *12*, 2968–2971; *Angew. Chem.* **2012**, *124*, 3022–3025; c) N. Kalutharage, C. S. Yi, *Angew. Chem. Int. Ed.* **2013**, *52*, 13651–13655; *Angew. Chem.* **2013**, *125*, 13896–13900; d) H. Huang, X. Ji, W. Wu, L. Huang, H. Jiang, *J. Org. Chem.* **2013**, *78*, 3774–3782; e) M.-G. Zhou, W.-Z. Zhang, S.-K. Tian, *Chem. Commun.* **2014**, *50*, 14531–14534.

[4] a) C. H. Basch, J. Liao, J. Xu, J. J. Piane, M. P. Watson, *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316; b) F. J. Klauck, M. J. James, F. Glorius, *Angew. Chem. Int. Ed.* **2017**, *56*, 12336–12339; c) J. Wang, M. E. Hoerrner, M. P. Watson, D. J. Weix, *Angew. Chem. Int. Ed.* **2020**, *59*, 13484–13489; *Angew. Chem.* **2020**, *132*, 13586–13591; d) S. Plunkett, C. H. Basch, S. O. Santana, M. P. Watson, *J. Am. Chem. Soc.* **2019**, *141*, 2257–2262.

[5] M. A. Ashley, T. Rovis, *J. Am. Chem. Soc.* **2020**, *142*, 18310–18316.

[6] S. Tang, M. Rauch, M. Montag, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2020**, *142*, 20875–20882.

[7] a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485–496; b) M. Alcarazo, S. J. Roseblade, A. R. Cowley, R. Fernández, J. M. Brown, J. M. Lassaletta, *J. Am. Chem. Soc.* **2005**, *127*, 3290–3291; c) F. E. Hahn, *Angew. Chem. Int. Ed.* **2006**, *45*, 1348–1352; d) N. Kundu, M. Maity, P. B. Chatterjee, S. J. Teat, A. Endo, M. Chaudhury, *J. Am. Chem. Soc.* **2011**, *133*, 20104–20107; e) M. D. Weber, C. Garino, G. Volpi, E. Casamassa, M. Milanesio, C. Barolo, R. D. Costa, *Dalton Trans.* **2016**, *45*, 8984–8993; f) D. Davey, P. W. Erhardt, W. C. Lumma Jr., J. Wiggins, M. Sullivan, D. Pang, E. Cantor, *J. Med. Chem.* **1987**, 1337–1342; g) L. Browne, C. Gude, H. Rodriguez, R. Steele, A. Bhatnager, *J. Med. Chem.* **1991**, *34*, 725–736; h) B. P. Fauber, A. Gobbi, K. Robarge, A. Zhou, A. Barnard, J. Cao, Y. Deng, C. Eidenschenk, A. Everett, A. Ganguli, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2907–2912.

[8] G. Volpi, R. Rabezzana, *New J. Chem.* **2021**, *45*, 5737–5743.

[9] a) G. Volpi, E. Priola, C. Garino, A. Daolio, R. Rabezzana, P. Benzi, A. Giordana, E. Diana, R. Gobetto, *Inorg. Chim. Acta* **2020**, *509*, 119662; b) G. Volpi, S. Galliano, R. Buscaino, G. Viscardi, C. Barolo, *J. Lumin.* **2022**, *242*, 118529; c) S. Priyanga, T. Khamrang, M. Velusamy, S. Karthi, B. Ashokkumar, R. Mayilmurugan, *Dalton Trans.* **2019**, *48*, 1489–1503.

[10] J. Wang, L. Dyers, R. Mason, P. Amoyaw, X. R. Bu, *J. Org. Chem.* **2005**, *70*, 2353–2356.

[11] G. Volpi, G. Magnano, I. Benesperi, D. Saccone, E. Priola, V. Gianotti, M. Milanesio, E. Conterosito, C. Barolo, G. Viscardi, *Dyes Pigm.* **2017**, *137*, 152–164.

[12] S. Chuprakov, F. W. Hwang, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2007**, *119*, 4841–4843; *Angew. Chem.* **2007**, *119*, 4841–4843.

[13] Y. Shi, A. V. Gulevich, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2014**, *53*, 14191–14195; *Angew. Chem.* **2014**, *126*, 14415–14419.

[14] a) H. Wang, W. Xu, L. Xin, W. Liu, Z. Wang, K. Xu, *J. Org. Chem.* **2016**, *81*, 3681–3687; b) M. Li, Y. Xie, Y. Ye, Y. Zou, H. Jiang, W. Zeng, *Org. Lett.* **2014**, *16*, 6232–6235.

[15] P. K. Singh, V. K. Singh, *Org. Lett.* **2008**, *10*, 4121–4124.

[16] a) H. Kunz, K. Rück, *Angew. Chem. Int. Ed.* **1993**, *32*, 336–358; b) M. Diéguez, O. Pàmies, C. Claver, *Chem. Rev.* **2004**, *104*, 3189–3216.

[17] F. Zhu, M. A. Walczak, *J. Am. Chem. Soc.* **2020**, *142*, 15127–15136.

[18] a) D. L. Bertuzzi, T. B. Becher, N. M. Capreti, J. Amorim, I. D. Jurberg, J. D. Megiatto Jr, C. Ornelas, *Global Chall.* **2018**, *2*, 1800046; b) C. Virués, J. Hernández, I. Higuera-Ciapara, E. Martínez-Benavidez, J. L. Olivares-Romero, R. E. Navarro, M. Inoue, *Carbohydr. Res.* **2020**, *490*, 107952.

[19] S. Rayne, K. Forest, *Nat. Preced.* **2010**, 1–1.

[20] D. W. Barnum, *J. Chem. Educ.* **1999**, *76*, 938.

[21] *Critical Stability Constants: Second Supplement* (Eds.: R. M. Smith, A. E. Martell), Springer, New York, **1989**, p. 513.

[22] R. N. Goldberg, N. Kishore, R. M. Lennen, *J. Phys. Chem. Ref. Data* **2002**, *31*, 231–370.

[23] T. Kida, S.-i. Sato, H. Yoshida, A. Teragaki, M. Akashi, *Chem. Commun.* **2014**, *50*, 14245–14248.

[24] P. Roose, K. Eller, E. Henkes, R. Rossbacher, H. Höke, *Ullmann's Encyclopedia of Industrial Chemistry: Amines, Aliphatic*, Wiley-VCH, Weinheim, **2000**, pp. 1–55.

[25] W. N. Olmstead, Z. Margolin, F. G. Bordwell, *J. Org. Chem.* **1980**, *45*, 3295–3299.

[26] L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* **2016**, *116*, 4006–4123.

[27] a) G. Büldt, H. Gally, A. Seelig, J. Seelig, G. Zaccai, *Nature* **1978**, *271*, 182–184; b) M. I. Blake, H. L. Crespi, J. J. Katz, *J. Pharm. Sci.* **1975**, *64*, 367–391; c) H. Geng, X. Chen, J. Gui, Y. Zhang, Z. Shen, P. Qian, J. Chen, S. Zhang, W. Wang, *Nat. Catal.* **2019**, *2*, 1071–1077; d) J. Su, X. Ma, Z. Ou, Q. Song, *ACS Cent. Sci.* **2020**.

[28] C. Schmidt, *Nat. Biotechnol.* **2017**, *35*, 493–495.

[29] E. R. Monteith, P. Mampuys, L. Summerton, J. H. Clark, B. U. Maes, C. R. McElroy, *Green Chem.* **2020**, *22*, 123–135.

[30] E. M. Pérez, M. Ávalos, R. Babiano, P. Cintas, M. E. Light, J. L. Jiménez, J. C. Palacios, A. Sancho, *Carbohydr. Res.* **2010**, *345*, 23–32.

[31] T. Jain, H. Kumar, P. K. Dutta in *Chitin and Chitosan for Regenerative Medicine* (Ed.: P. Dutta), Springer, New Delhi, **2016**, pp. 279–295.

[32] C.-H. Dang, C.-H. Nguyen, T.-D. Nguyen, C. Im, *RSC Adv.* **2014**, *4*, 6239–6245.

[33] M. Kim, S. Kang, Y. H. Rhee, *Angew. Chem. Int. Ed.* **2016**, *55*, 9733–9737; *Angew. Chem.* **2016**, *128*, 9885–9889.

[34] C.-A. Omar, S.-P. Fernando, *Carbohydr. Res.* **2021**, *510*, 108441.

[35] A. V. Dass, T. Georgelin, F. Westall, F. Foucher, P. De Los Rios, D. M. Busiello, S. Liang, F. Piazza, *Nat. Commun.* **2021**, *12*, 1–10.

[36] K. Nester, K. Gaweda, W. Plazinski, *J. Chem. Theory Comput.* **2019**, *15*, 1168–1186.

[37] J. T. Hutt, J. Jo, A. Olasz, C.-H. Chen, D. Lee, Z. D. Aron, *Org. Lett.* **2012**, *14*, 3162–3165.

[38] a) J. Zeng, R. Wang, S. Zhang, J. Fang, S. Liu, G. Sun, B. Xu, Y. Xiao, D. Fu, W. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 8509–8515; b) E. Patyk, A. Katrusiak, *Chem. Sci.* **2015**, *6*, 1991–1995; c) F. Zhu, M. A. Walczak, *J. Am. Chem. Soc.* **2020**, *142*, 10.

[39] J. Wang, R. Mason, D. VanDerveer, K. Feng, X. R. Bu, *J. Org. Chem.* **2003**, *68*, 5415–5418.

[40] T. H. Meyer, W. Liu, M. Feldt, A. Wuttke, R. A. Mata, L. Ackermann, *Chem. Eur. J.* **2017**, *23*, 5443–5447.