Anomeric stereoauxiliary strategy enables efficient synthesis of wide-ranging imidazo[1,5-a]pyridines

Kui Zeng

University of Göttingen

Jin Ye

University of Goettingen

Xintong Meng

University of Goettingen

Sebastian Dechert

University of Goettingen <https://orcid.org/0000-0002-2864-2449>

Martin Simon

University of Goettingen

Shuaiyu Gong

University of Goettingen

Ricardo Mata

University of Goettingen

Kai Zhang (✉ kai.zhang@uni-goettingen.de)

University of Göttingen

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Abstract

Imidazo[1,5-*a*]pyridines are one of the most important groups of *N*-heterocyclic compounds, with wide applications in pharmaceuticals, chemical science and material science. Despite tremendous progress in their synthesis over the past decade, a number of important imidazo[1,5-*a*]pyridines as intermediate products remain inaccessible, such as 1-alkylimidazo[1,5-*a*]pyridines. Herein, we report a novel anomeric stereoauxiliary approach for the preparation of this important class of compounds. It strongly expands the scope of readily accessible imidazo[1,5-*a*]pyridines well beyond the existing state-of-the-art methods. More than 80 products with a substantial number of deemed unattainable ones were synthesized. With the first time accessibility to alkyl(pyridine-2-yl)methanone substrates, a group of important deuterated imidazo[1,5-*a*]pyridines derivatives were also efficiently achieved. The mechanism containing a key seven-membered ring transition state via α -anomeric stereoauxiliary for this new synthetic pathway is provided in great detail and supported by electronic structure calculations. In total, this novel synthetic approach for a broad range of imidazo[1,5-*a*]pyridines involving the native stereochemistry will open a new window for research endeavors in diverse fields, encompassing organic synthesis, biomass conversion via cleavage of C-N bonds and medicinal chemistry.

Main Text

Imidazo[1,5-*a*]pyridines, one of the most important group of *N*-heterocyclic compounds, play a pivotal role from pharmaceuticals over chemical science to material science.¹⁻⁸ For example, they can be precursors of *N*-heterocyclic carbenes,¹⁻³ ligands in coordination chemistry,^{4,5} and inhibitors of biologically active agents.⁶⁻⁸ In this respect, advances from metal-free to metal-catalyzed cyclization strategies of *N*-heterocyclic substrates have expanded the chemical space of accessible structures (Fig. 1a). The representative metal-free method with utilization of NH₄OAc as nitrogen source for imidazo[1,5-*a*]pyridines was reported in 2005 (Fig. 1a).⁹ This method was continually improved and widely used in synthetic chemistry and optical materials¹⁰ even though the challenges including inaccessible 1-alkylimidazo[1,5-*a*]pyridines and 3-alkylimidazo[1,5-*a*]pyridines products still need to be improved.

In 2007, Gevorgyan's group reported the first efficient rhodium-catalyzed metal carbene approach for the preparation of imidazo[1,5-*a*]pyridines via transannulation of pyridotriazoles process (Fig. 1a).¹¹ 3-alkylimidazo[1,5-*a*]pyridines products with 6 examples were first time accessible by this metal-catalyzed method. It was shown that activating group (Cl, Br, or OMe substituents) at C₇, as well as electron-withdrawing groups at C₃, were requisite for efficient formation of the imidazo[1,5-*a*]pyridines. To overcome these limitations, in 2014, they developed the general rhodium-catalyzed NH insertion of pyridyl carbenes strategy for imidazo[1,5-*a*]pyridines (Fig. 1a).¹² Although this strategy widely expanded the chemical space of accessible structures, the only 6 examples in total and the required precious metal catalyst with active triazoles substrates still hinder its broad applications. In 2014 and 2016, inexpensive copper catalysts were first used for imidazo[1,5-*a*]pyridines and a range of imidazo[1,5-*a*]pyridines were prepared. These methods are inaccessible to 1-alkylimidazo[1,5-*a*]pyridines products^{13,14} and limited to 3-

monosubstituted imidazo[1,5-*a*]pyridines.¹⁴ The challenges for accessible to 1-alkylimidazo[1,5-*a*]pyridines via ketone activation of alkyl(pyridine-2-yl)methanone substrates is because of the less reaction reactivity of alkyl(pyridine-2-yl)methanone than aryl(pyridine-2-yl)methanone.¹³ Besides, alkyl(pyridine-2-yl)methanone with the α -saturated C-H bond of ketone is easily activated as nucleophilic reagent, which can result in side-reactions.¹⁵ Therefore, it is highly desired to develop a strategy to surpass these drawbacks.

Carbohydrates as chiral auxiliaries in stereoselective synthesis^{16,17} and stereochemistry of transition metal complexes controlled by the metallo-anomeric effect¹⁸ have drawn much attention until today. Depending on the suitable pK_a aqueous solution, the α / β -anomers of D-glucosamine exist with adjustable ratios.^{19,20} Inspired by these different stereochemical structures of α / β -anomers, we report herein an novel anomeric stereoauxiliary approach for the preparation of these important class of imidazo[1,5-*a*]pyridines which expands the scope of readily accessible products (more than 80) relative to existing state-of-the-art methods (Fig. 1b).

Reaction development. 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 (Supplementary Table 1 and Fig. 2a). After extensive experimentation, we got the optimal condition for the efficient synthesis of imidazo[1,5-*a*]pyridines of 74% yield with D-glucosamine as nitrogen source in the solvent mixtures ($v_{\text{AcOH}}:v_{\text{H}_2\text{O}}$ of 9:1) at 120 °C under Ar gas atmosphere (Fig. 2a). Then, the commercial acetylated amine sugars as stabilized α -anomer (**3b**) and β -anomer (**3c**) were used for the reactions under the optimal conditions (Fig. 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 hydroxyl group at the neighbor C1 position should play an important role for 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 ($\alpha/\beta = 0.79/1$). This result further verified that the configuration of amine and hydroxyl 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 scoped. As a result, only **3e** fulfilling these configuration requirements generated the highest yield of 16%.

To explore the correlation between the yield of imidazo[1,5-*a*]pyridines **4** and the anomer of D-glucosamine in solvents with diverse pK_a, solvent mixtures with various pK_a (0.9 mL) and H₂O (0.1 mL) were investigated under the optimal conditions (Fig. 2b). It should be noted that the ratio between α - and β -anomer of D-glucosamine (refers as α/β) highly depends on the pK_a of solvents. Solvents with higher pK_a, such as HFIP (pK_a: 9.30), Et₃N (pK_a: 10.76) and H₂O (pK_a: 15.75), result in lower α/β ratios of glucosamine and significantly lower yields of imidazo[1,5-*a*]pyridines **4**. The predominant reason should be the presence of majorly the β -anomer of D-glucosamine. In comparison, those suitable acidic conditions, such as CF₃COOH (pK_a: 0.30), HCOOH (pK_a: 3.75) and AcOH (pK_a: 4.76), achieve higher α/β ratios of glucosamine and lead to higher yields of **4**, showing the facilitating effect of the α -anomer of D-glucosamine for the synthesis of **4**. These results further indicate the Brønsted acids with suitable pK_a to

stabilize the methyl group of alkyl(pyridine-2-yl)methanone, and to hinder the deprotonation of the methyl group.²⁸

Substrate scope. With the optimized reaction conditions in hand, we first probed the scope of various aldehydes amenable to this process using 2-acetylpyridine as a representative heteroaryl ketones (Fig. 3). An array of aromatic aldehydes, including those with electron-donating or -withdrawing groups at different positions (*ortho*, *meta* or *para*), was used for the efficient transformation into corresponding products **4-23**. A variety of common functional groups at diverse positions, such as methoxyl (**11** and **12**), halogens (**14-18**), trifluoromethyl (**19**), nitro (**20**), nitrile (**21**) and ester (**22**), were well compatible with these conditions. It is noteworthy that free *para*-dialdehyde (**23**) and *ortho*-phenolic hydroxyl (**13**) were also tolerated in this protocol. The structure of **20** was determined by X-ray crystallographic analysis, and those of other products in Fig. 3 and 4 were assigned by analogy. Moreover, 2-phenylacetaldehyde (product **24**), cinnamaldehyde (product **25**), 1-naphthaldehyde (product **26**) and heterocyclic aldehydes (product **27-28**) were also well compatible with this reaction approach. Furthermore, a series of aliphatic aldehydes, including cyclic aldehydes (product **29-30**) and aliphatic chain aldehydes (product **31-34**), could also be transformed into corresponding products.

We further explored heteroaryl ketones derivatives (Fig. 4). Di(pyridin-2-yl)methanone (product **35**) and pyridin-2-yl(pyridin-4-yl)methanone (product **36**) were tolerated in this reaction approach. Various aromatic pyridine ketones, including those having electron-donating or -withdrawing groups at distinct positions (*ortho*, *meta* or *para*), could be well transformed into the corresponding products **37-43**. The functional groups at diverse phenyl ring positions, such as methyl (**38-39**), methoxyl (**40**), trifluoromethyl (**41**), mono-Br- (**42**) and di-Br-substituted phenyl ring (**43**), were all compatible with these conditions. The cyclic aliphatic pyridine ketone was also tolerated in these reaction conditions (**44**). In addition, this reaction approach also successfully included diverse bidentate (**48-60**), tridentate ligands (**45-47**) and heterocyclic backbones with fluorescence. The structure of **51** was determined by X-ray crystallographic analysis.

Synthetic applications. Certain imidazo[1,5-*a*]pyridines with multiple substitutions have interesting optical properties and ligand effects due to the conjugation 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. In our method, bi-functionalization of dialdehyde (product **61**) substantially took place after 3 days (Fig. 5a). Motivated by this result, the 1,4-phenylenebis(pyridin-2-yl)methanone (product **62**) was also prepared via the same synthesis route after 3 days (Fig. 5b). 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. Moreover, 11-methyl-6,7,8,9-tetrahydroimidazo[1,2-*a*:3,4-*a'*]dipyridin-10-ium (**65**) was yielded after two steps synthesis under standard conditions.

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.²⁹⁻³² The first deuterated drug, deutetrabenazine, was approved by FDA in 2017.³³ Because of the versatile functionalities of imidazo[1,5-*a*]pyridines that are interesting for diverse fields ranging from material science to pharmaceuticals, efficient synthetic methods for deuterated 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 protons with acidic aqueous surroundings (Supplementary Fig. 18-19). Therefore, in our work, deuterated imidazo[1,5-*a*]pyridines were readily synthesized via one-pot process with the simultaneous cleavage of 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 for **66-81** (Fig. 6). 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.

Mechanistic considerations. To gain insight into the mechanism, four groups of control experiments were conducted (Fig. 7 and 8). First, intermediates **3j** and **3k** were used to verify the reaction order (Group 1 in Fig. 7a-7b).^{34,35} As a result, product **13** was detected via ¹H-NMR spectra and confirmed via HR-ESI-MS spectra (Group 1 in Fig. 7a), while product **4** was not detectable (Group 1 in Fig. 7b). Therefore, D-glucosamine should have reacted with aldehyde at first to form the imine intermediate.

In the second group control experiment, *N*-acetyl-D-glucosamine was scoped under standard conditions (Group 2 in Fig. 7c). The results excluded the cleavage pathway via *N*-acetylation of D-glucosamine, and also revealed that amine should react with reactants without acetylation. In the absence of aldehyde and 2-acetylpyridine, only traces of ammonium acetate were determined via ¹H-NMR analysis (Group 2 in Fig. 7d) and verified by two-dimensional ¹H-¹⁵N-heteronuclear single quantum coherence (HSQC)-NMR measurement (Supplementary Fig. 10-11), which excluded the pathway of thermo-cleavage of the C-N bond in D-glucosamine. Moreover, the intermediates **3o**, **3p**, **3q** and **5** were detected by HR-ESI-MS and ESI-MS, which reveals 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 D-glucosamine (Group 2 in Fig. 7e). 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 (Group 2 in Fig. 7f).³⁶

In further control groups, 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- β -D-glucopyranose hydrochloride (**3b**) and 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy- α -D-glucopyranose hydrochloride (**3c**) were tested under the same conditions (Group 3 in Fig. 8a-8b). As a result, the product **4** with 30% yield was obtained using **3c** (α -anomer), while **3b** (β -anomer) could only achieve 8% yield of product **4**. Based on the results shown in Fig. 7, plausible reaction pathways for TS _{α} and TS _{β} are proposed in Fig. 8 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 (Fig. 8a). Moreover, the α -anomer promotes the formation of a seven-membered ring transition state with the acetate anion in

solutions via hydrogen bonds. This ring of the α -anomer transition state (TS_α) not only could help to stabilize the intermediate during the cleavage of the C-N bond, but also shows a favourable alignment with the aromatic ring. With the **3b** (β -anomer) (Fig. 8b), a seven-membered ring transition state under β -anomer forms via a hydrogen bond between the acetyl group of the β -anomer and the acetate anion. The *E* isomer of imine is easier to form,³⁵ especially the stronger steric shielding from seven-membered ring transition state. The ring of the β -anomer transition state (TS_β) shows a disfavourable alignment with aromatic ring. The energy states of both TS_α and TS_β were calculated by electronic structure calculations (Fig. 9b).

Proposed mechanism. Hence, based on the results shown in Fig. 2, 7 and 8, a seven-membered ring of α -anomer transition state (TS_α) should be formed via hydrogen bonds, which favors the following cleavage of the C-N bond.³⁷⁻³⁹ Combining all results, a plausible mechanism is proposed (Fig. 9a). First, D-glucosamine reacts with aldehyde to form imine **A**. Then, **A** attacks the ketone of pyridine ketone via electrophilic addition to generate the intermediate **B**.⁴⁰ Under acidic conditions with acetic acid, a seven-membered ring of α -anomer transition state (TS_α) forms. The nitrogen of pyridine attacks the imine via nucleophilic addition to form the intermediate **C**. Under acidic conditions, the intermediate **D** forms via dehydration. The seven-membered ring of α -anomer transition state (TS_α) 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 favourable alignment with the seven-membered ring. Due to the unstable transition state of **F**, **H** forms quickly via 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_α in Fig. 9b) was 0.9 kcal/mol lower than that of the β -anomer (TS_β). Since the reactant connected to TS_α (**D α**) was 0.7 kcal/mol higher than that connected to TS_β (**D β**), the reaction barrier of the α -anomer is thus 1.6 kcal/mol 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 taken as the actual barrier difference. The acetate molecule stabilizes the transition state via the hydrogen bond as depicted in Fig. 5a, which is ultimately transferred. The ring system, as schematically shown in Fig. 5b, aligns with the carboxylic group, with dispersion forces reducing the barrier. This stands as a further example for the importance of London forces in stereoselectivity.⁴¹

The α/β -ratio for the mixture of D-glucosamine and HCl was determined using the same theoretical method. Three conformers (Fig. 9c) 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 Fig. 9c. 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.

In summary, we have developed a novel α -anomeric stereoauxiliary strategy to efficiently access to diverse imidazo[1,5-*a*]pyridines products (more than 80). This includes important with/without - deuterated 1-alkylimidazo[1,5-*a*]pyridines. Control experiments and DFT calculations revealed that a seven-membered ring in the α -anomer transition state (TS α) formed in situ facilitates the cleavage of C-N bonds and was stabilized by dispersion interactions to a neighboring aromatic ring. We believe that this approach for the synthesis of imidazo[1,5-*a*]pyridines by using native stereochemistry of D-glucosamine will be of significant and general interest for chemical synthesis.

Methods

Preparation of imidazol [1,5-*a*]pyridines.

Method B: A mixture of pyridine ketone (0.1 mmol), aldehydes (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H₂O (0.9 mL : 0.1 mL) was stirred at 120 °C under Ar atmosphere for 36 h.

Method C: A mixture of pyridine ketone (0.1 mmol), aldehydes (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H₂O (0.9 mL : 0.1 mL) was stirred at 120 °C under Ar atmosphere for 36 h.

Workup: The reactions were conducted in a sealed Schlenk tube 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 basified up to pH 7 using Na₂CO₃ aqueous solution, extracted by diether (3×3 mL) and dried over anhydrous Na₂SO₄. After filtration and concentration on 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 the same procedure B in AcOH-d₄ : D₂O (0.9 mL : 0.1 mL) solvent.

Declarations

Data availability

The data that support the findings of this study are available in the Supplementary Information (experimental procedures and characterization data). Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as CCDC 2068036 (**20**) and 2068037 (**51**) and can be obtained free of charge from the CCDC via www.ccdc.cam.ac.uk/structures.

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Author Contributions

K. Zhang conceived the concept and supervised the project. K. Zeng designed and performed the experiments. J. Ye and R. Mata analyzed DFT calculation. S. Dechert measured and analyzed the single crystal structures. M. Simon helped to measure and analyze the molecular mass via GC-MS. K. Zeng, X. Meng and S. Gong analyzed the melting points and FT-IR spectra of all unknown products. K. Zeng and K. Zhang analyzed and discussed the experimental data. K. Zeng and K. Zhang drafted the manuscript. All authors discussed the results and revised the manuscript.

Competing interests

The authors declare no competing interests.

References

- 1 Hopkinson, M. N., Richter, C., Schedler, M. & Glorius, F. An overview of *N*-heterocyclic carbenes. *Nature* **510**, 485-496 (2014).
- 2 Alcarazo, M. *et al.* Imidazo [1, 5-a] pyridine: a versatile architecture for stable *N*-heterocyclic carbenes. *J. Am. Chem. Soc.* **127**, 3290-3291 (2005).
- 3 Hahn, F. E. Heterocyclic carbenes. *Angew. Chem., Int. Ed.* **45**, 1348-1352 (2006).
- 4 Kundu, N. *et al.* Reporting a unique example of electronic bistability observed in the form of valence tautomerism with a copper (II) helicate of a redox-active nitrogenous heterocyclic ligand. *J. Am. Chem. Soc.* **133**, 20104-20107 (2011).

- 5 Weber, M. D. *et al.* Origin of a counterintuitive yellow light-emitting electrochemical cell based on a blue-emitting heteroleptic copper (I) complex. *Dalton Trans.* **45**, 8984-8993 (2016).
- 6 David Davey, P. W. E. W. C. L., Jr., Jay Wiggins, Mark Sullivan, David Pang, & Cantor, a. E. <Cardiotonic Agents. 1. Novel 8-Aryl-Substituted Imidazo[1,2-a]- and -[1,5-a]pyridines and Imidazo[l,5-a]pyridinones as Potential Positive Inotropic Agents>. *J. Med. Chem.*, 1337-1342 (1987).
- 7 Browne, L., Gude, C., Rodriguez, H., Steele, R. & Bhatnager, A. Fadrozole hydrochloride: a potent, selective, nonsteroidal inhibitor of aromatase for the treatment of estrogen-dependent disease. *J. Med. Chem.* **34**, 725-736 (1991).
- 8 Fauber, B. P. *et al.* Discovery of imidazo [1, 5-a] pyridines and-pyrimidines as potent and selective RORc inverse agonists. *Bioorg. Med. Chem. Lett.* **25**, 2907-2912 (2015).
- 9 Wang, J., Dyers, L., Mason, R., Amoyaw, P. & Bu, X. R. Highly efficient and direct heterocyclization of dipyrityl ketone to N, N-bidentate ligands. *J. Org. Chem.* **70**, 2353-2356 (2005).
- 10 Volpi, G. *et al.* One pot synthesis of low cost emitters with large Stokes' shift. *Dyes Pigm.* **137**, 152-164 (2017).
- 11 Chuprakov, S., Hwang, F. W. & Gevorgyan, V. Rh-Catalyzed Transannulation of Pyridotriazoles with Alkynes and Nitriles. *Angew. Chem., Int. Ed.* **119**, 4841-4843 (2007).
- 12 Shi, Y., Gulevich, A. V. & Gevorgyan, V. Rhodium-Catalyzed NH Insertion of Pyridyl Carbenes Derived from Pyridotriazoles: A General and Efficient Approach to 2-Picolylamines and Imidazo [1, 5-a] pyridines. *Angew. Chem., Int. Ed.* **53**, 14191-14195 (2014).
- 13 Wang, H. *et al.* Synthesis of 1, 3-disubstituted imidazo [1, 5-a] pyridines from amino acids via catalytic decarboxylative intramolecular cyclization. *J. Org. Chem.* **81**, 3681-3687 (2016).
- 14 Li, M. *et al.* Cu (I)-Catalyzed Transannulation of *N*-Heteroaryl Aldehydes or Ketones with Alkylamines via C (sp³)–H Amination. *Org. Lett.* **16**, 6232-6235 (2014).
- 15 Singh, P. K. & Singh, V. K. Highly Enantioselective Friedel– Crafts Reaction of Indoles with 2-EnoylPyridine 1-Oxides Catalyzed by Chiral Pyridine 2, 6-Bis (5', 5'-diphenyloxazoline)–Cu (II) Complexes. *Org. Lett.* **10**, 4121-4124 (2008).
- 16 Kunz, H. & Rück, K. Carbohydrates as chiral auxiliaries in stereoselective synthesis. New synthetic methods (90). *Angew. Chem., Int. Ed.* **32**, 336-358 (1993).
- 17 Diéguez, M., Pàmies, O. & Claver, C. Ligands derived from carbohydrates for asymmetric catalysis. *Chem. Rev.* **104**, 3189-3216 (2004).

- 18 Zhu, F. & Walczak, M. A. Stereochemistry of transition metal complexes controlled by the metallo-anomeric effect. *J. Am. Chem. Soc.* **142**, 15127-15136 (2020).
- 19 Bertuzzi, D. L. *et al.* General Protocol to Obtain D-Glucosamine from Biomass Residues: Shrimp Shells, Cicada Sloughs and Cockroaches. *Glob. Chall.* **2**, 1800046 (2018).
- 20 Virués, C. *et al.* Formulation of anomerization and protonation in d-glucosamine, based on ¹H NMR. *Carbohydr. Res.* **490**, 107952 (2020).
- 21 Rayne, S. & Forest, K. Theoretical studies on the pK_a values of perfluoroalkyl carboxylic acids. *Nat. Preced.*, 1-1 (2010).
- 22 Barnum, D. W. Predicting acid-base titration curves without calculations. *J. Chem. Educ.* **76**, 938 (1999).
- 23 Smith, R. M. & Martell, A. E. *Critical stability constants: second supplement.* (Springer, 1989).
- 24 Goldberg, R. N., Kishore, N. & Lennen, R. M. Thermodynamic quantities for the ionization reactions of buffers. *J. Phys. Chem. Ref. Data* **31**, 231-370 (2002).
- 25 Kida, T., Sato, S.-i., Yoshida, H., Teragaki, A. & Akashi, M. 1, 1, 1, 3, 3, 3-Hexafluoro-2-propanol (HFIP) as a novel and effective solvent to facilely prepare cyclodextrin-assembled materials. *Chem. Commun.* **50**, 14245-14248 (2014).
- 26 Roose, P., Eller, K., Henkes, E., Rossbacher, R. & Höke, H. Amines, aliphatic. *Ullmann's Encyclopedia of Industrial Chemistry*, 1-55 (2000).
- 27 Olmstead, W. N., Margolin, Z. & Bordwell, F. G. Acidities of water and simple alcohols in dimethyl sulfoxide solution. *J. Org. Chem.* **45**, 3295-3299 (1980).
- 28 Hong, L., Sun, W., Yang, D., Li, G. & Wang, R. Additive effects on asymmetric catalysis. *Chem. Rev.* **116**, 4006-4123 (2016).
- 29 Büldt, G., Gally, H., Seelig, A., Seelig, J. & Zaccai, G. Neutron diffraction studies on selectively deuterated phospholipid bilayers. *Nature* **271**, 182-184 (1978).
- 30 Blake, M. I., Crespi, H. L. & Katz, J. J. Studies with deuterated drugs. *J. Pharm. Sci.* **64**, 367-391 (1975).
- 31 Geng, H. *et al.* Practical synthesis of C1 deuterated aldehydes enabled by NHC catalysis. *Nat. Catal.* **2**, 1071-1077 (2019).
- 32 Su, J., Ma, X., Ou, Z. & Song, Q. Deconstructive Functionalizations of Unstrained Carbon–Nitrogen Cleavage Enabled by Difluorocarbene. *ACS Cent. Sci.* (2020).

- 33 Schmidt, C. (Nature Publishing Group, 2017).
- 34 Dang, C.-H., Nguyen, C.-H., Nguyen, T.-D. & Im, C. Synthesis and characterization of N-acyl-tetra-O-acyl glucosamine derivatives. *RSC Adv.* **4**, 6239-6245 (2014).
- 35 Pérez, E. M. *et al.* Schiff bases from d-glucosamine and aliphatic ketones. *Carbohydr. Res.* **345**, 23-32 (2010).
- 36 Hutt, J. T. *et al.* Fluorescence switching of imidazo [1, 5-a] pyridinium ions: pH-sensors with dual emission pathways. *Org. Lett.* **14**, 3162-3165 (2012).
- 37 Zeng, J. *et al.* Hydrogen-bonding-assisted exogenous nucleophilic reagent effect for β -selective glycosylation of rare 3-amino sugars. *J. Am. Chem. Soc.* **141**, 8509-8515 (2019).
- 38 Patyk, E. & Katrusiak, A. Transformable H-bonds and conformation in compressed glucose. *Chem. Sci.* **6**, 1991-1995 (2015).
- 39 Zhu, F. & Walczak, M. A. Stereochemistry of transition metal complexes controlled by the metallo-anomeric effect. *J. Am. Chem. Soc.* **142**, 10 (2020).
- 40 Wang, J., Mason, R., VanDerveer, D., Feng, K. & Bu, X. R. Convenient preparation of a novel class of imidazo [1, 5-a] pyridines: decisive role by ammonium acetate in chemoselectivity. *J. Org. Chem.* **68**, 5415-5418 (2003).
- 41 Meyer, T. H. *et al.* Manganese (I)-Catalyzed Dispersion-Enabled C–H/C–C Activation. *Chem. Eur. J.* **23**, 5443-5447 (2017).

Figures

Figure 1

Diverse methods for imidazo[1,5-a]pyridines. a The representative example of previous strategies for the preparation of imidazo[1,5-a]pyridines. b Our strategy through anomeric stereoauxiliary cleavage of C-N bond for imidazo[1,5-a]pyridines.

Figure 2

Reaction development. a Diverse amino compounds 3a-3i were used in reactions in the solvent mixtures (vAcOH:vH₂O of 9:1) at 120 °C under Ar gas atmosphere. b Various mixtures of solvents with various pKa (0.9 mL) and H₂O (0.1 mL) were used for the reactions under the optimal conditions. pKa of CF₃COOH,²¹ H₃PO₄,²² HCOOH,²³ CH₃COOH,²⁴ 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),²⁵ Et₃N,²⁶ and H₂O²⁷ are determined at 25 °C. The ratios of α - and β -anomers were measured by ¹H-NMR analysis at room temperature; Yields were determined by ¹H-NMR analysis with CH₂Br₂ as the internal standard.

Figure 3

Substrate scope of aldehydes. Reactions were carried out at 120 °C with 2-acetylpyridine, aldehyde, D-glucosamine·HCl (3a) in AcOH : H₂O (0.9 mL : 0.1 mL), under Ar gas with stirring for 36 h. Yields are those of the isolated product.

Figure 4

Substrate scope of N-heteroaryl ketones and aldehydes. Reactions were carried out at 120 °C with N-heteroaryl ketones, aldehydes, D-glucosamine·HCl (3a) in AcOH : H₂O (0.9 mL : 0.1 mL), under Ar gas with stirring for 36 h. Yields are those of the isolated product.

Figure 5

Synthetic applications. a, b Multi-transformations of aldehyde and N-heteroaryl ketone. c, d, e Late-stage transformation of imidazo[1,5-a]pyridine.

Figure 6

One-pot synthetic applications for diverse deuterated imidazo[1,5-a]pyridines. All yields are isolated products and the D incorporation was measured by ¹H-NMR analysis.

Figure 7

Mechanistic studies of reaction pathway control experiments. a, b Reaction intermediate control experiments. c N-acetyl-D-glucosamine instead of D-glucosamine under standard reaction conditions. d Deamination effect of D-glucosamine under standard reaction conditions. e ESI analysis of 4 intermediates under standard reaction conditions. f Disfavored pathway of post dealkylation of imidazo[1,5-a]pyridinium salts.

Figure 8

Mechanistic studies of anomeric stereoauxiliary control experiments. a A favourable alignment shows when using α -acetyl-glucosamine (3c). b A disfavoured alignment shows when using β -acetyl-glucosamine (3b).

Figure 9

a Proposed mechanism. b Density functional theory calculations for the step reaction of D intermediate of Fig. 5a to intermediates E and H. 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.

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