N-Containing Biomass for the Sustainable Synthesis of *N*-Heterocycles *via* Cyclization Reactions

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Abstract

The *N*-containing compounds from biomass, including chitin, chitosan and D-glucosamine, are one of the largest sustainable native biobased materials on earth. Human processing of the sustainable chitin/chitosan/D-glucosamine-containing raw materials exhibits only a very minor fraction of all the chitin produced annually in nature, while the major fraction maintains intact. In order to reduce the high reliance on non-renewable feedstocks, chitin/chitosan/D-glucosamine as a substitute has been increasingly utilized for value-added functional materials and important chemical feedstocks through diverse routes, mainly including chemical modifications, transformations, as ligands or catalysts in organic synthetic pathways. Despite the tremendous progress on the usage of the *N*-containing biomass, it is still a great challenge to directly utilize it to prepare important *N*-heterocyclic compounds though cyclization reactions.

The targeted cleavage of C−N bonds of alkyl primary amines in chitin, chitosan and D-glucosamine *via* a metal-free pathway and the conjunction of nitrogen in the synthesis of imidazo[1,5-a]pyridines are still highly challenging. In publication 1, we reported 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 is capable of C−N bond cleavage through a seven-membered ring transition state. Using this novel method, a series of imidazo[1,5-a]pyridine derivatives (more than 80 examples) were synthesized from pyridine ketones (including para-dipyridine ketone) and aldehydes (including para-dialdehyde). Moreover, imidazo[1,5-a]pyridines derivatives containing diverse important deuterated $C(sp^2)$−H and $C(sp^3)$−H bonds were also efficiently achieved.

In publication 2, we discribed a facile and efficient one-pot methodology that enables nitrogen interception directly from chitosan/chitin for the synthesis of a broad range of important *N*-heterocycles imidazo[1,5-a]pyridines (52 examples). This strategy is featured by directly synthesizing tridentate ligands and important deuterated imidazo[1,5-a]pyridines. In particular, an extended range of various functional moieties on imidazo[1,5-a]pyridine backbone are tolerated with high efficiency under these mild and catalyst-free conditions.

Diverse aminocatalysis modes have been discovered over the last decades, while sustainable aminocatalyst with native chiral skeleton from biomass for the regioselective annulations reaction are highly desirable but not realized yet. In publication 3, a stereoauxiliary aminocatalysis strategy from β-anomeric glucosamine was achieved through the regioselective annulation of pyridine ketone with α,β-

unsaturated aldehyde for the construction of trisubstituted indolizine-2-carbaldehydes. Using our strategy with native chiral skeleton for the regioselective control, a highly expanded range of commercially available but oxidatively sensitive α,β-unsaturated aldehydes can act as coupling partners for the efficient preparation of readily accessible trisubstituted indolizine-2-carbaldehydes *via* one-pot pathway.

The thesis is a cumulative work with 3 publications. Two of them are published in peer-reviewed journals and the third one is in preparation. The background, the objective of the studies, results, discussions, general conclusions, perspectives and experimental section are shown in sections 1-5.

Zusammenfassung

Die N-haltigen Verbindungen aus Biomasse, darunter Chitin, Chitosan und D-Glucosamin, sind eines der größten nachhaltigen nativen biobasierten Materialien der Erde. Die menschliche Verarbeitung der nachhaltigen Chitin/Chitosan/D-Glucosamin-haltigen Rohstoffe weist nur einen sehr geringen Teil des jährlich in der Natur produzierten Chitins auf, während der Hauptteil intakt bleibt. Um die hohe Abhängigkeit von nicht erneuerbaren Rohstoffen zu verringern, wurde Chitin/Chitosan/D-Glucosamin als Ersatz zunehmend für wertsteigernde funktionelle Materialien und wichtige chemische Rohstoffe auf verschiedenen Wegen verwendet, hauptsächlich einschließlich chemischer Modifikationen, Transformationen, als Liganden oder Katalysatoren in organischen Synthesewegen. Trotz der enormen Fortschritte bei der Nutzung der N-haltigen Biomasse ist es immer noch eine große Herausforderung, sie direkt zu nutzen, um wichtige N-heterocyclische Verbindungen durch Cyclisierungsreaktionen herzustellen.

Die gezielte Spaltung von C-N-Bindungen von primären Alkylaminen in Chitin, Chitosan und D-Glucosamin über einen metallfreien Weg und die Bindung von Stickstoff in der Synthese von Imidazo[1,5-a]pyridinen stellen nach wie vor eine Aufgabe für die aktuelle Forschung dar. In Publikation 1 berichteten wir über einen anomeren Stereoauxiliar-Ansatz für die Synthese einer breiten Palette von Imidazo[1,5-a]pyridinen nach Spaltung der C-N-Bindung von D-Glucosamin (α-2°-Amin) aus biobasierten Ressourcen. Dieser neue Ansatz erweitert den Anwendungsbereich leicht zugänglicher Imidazo[1,5-a]pyridine im Vergleich zu bestehenden Methoden nach dem Stand der Technik. Ein entscheidender strategischer Vorteil dieses Ansatzes besteht darin, dass das α-Anomer von D-Glucosamin über einen siebengliedrigen Ringübergangszustand zur C-N-Bindungsspaltung fähig ist. Mit dieser neuartigen Methode wurde eine Reihe von Imidazo[1,5-a]pyridin-Derivaten (mehr als 80 Beispiele) aus Pyridinketonen (einschließlich para-Dipyridinketon) und Aldehyden (einschließlich para-Dialdehyd)

synthetisiert. Darüber hinaus wurden auch Imidazo[1,5-a]pyridine-Derivate mit verschiedenen wichtigen deuterierten C(sp^2)-H- und C(sp^3)-H-Bindungen effizient erhalten.

In Veröffentlichung 2 haben wir eine einfache und effiziente Eintopfmethode beschrieben, die das Abfangen von Stickstoff direkt aus Chitosan/Chitin für die Synthese einer breiten Palette wichtiger N-Heterocyclen Imidazo[1,5-a]pyridine (52 Beispiele) ermöglicht. Diese Strategie zeichnet sich durch die direkte Synthese von dreizähnigen Liganden und wichtigen deuterierten Imidazo[1,5-a]pyridinen aus. Insbesondere wird unter diesen milden und katalysatorfreien Bedingungen ein breiter Bereich verschiedener funktioneller Einheiten am Imidazo[1,5-a]pyridin-Rückgrat mit hoher Effizienz toleriert.

In den letzten Jahrzehnten wurden verschiedene Arten der Aminokatalyse entdeckt, während nachhaltige Aminokatalysatoren mit nativem chiralem Gerüst aus Biomasse für die regioselektive Anellierungsreaktion sehr wünschenswert, aber noch nicht realisiert sind. In Publikation 3 wurde eine stereoauxiliäre Aminokatalysestrategie ausgehend von β-anomerem Glucosamin durch die regioselektive Anellierung von Pyridinketon mit α,β-ungesättigtem Aldehyd zum Aufbau trisubstituierter Indolizin-2-carbaldehyde erreicht. Unter Verwendung unserer Strategie mit nativem chiralem Gerüst zur regioselektiven Steuerung kann eine stark erweiterte Palette kommerziell erhältlicher, aber oxidativ empfindlicher α,β-ungesättigter Aldehyde als Kupplungspartner für die effiziente Herstellung von leicht zugänglichen trisubstituierten Indolizin-2-carbaldehyden im Eintopfverfahren fungieren Weg.

Die Dissertation ist eine kumulative Arbeit mit 3 Publikationen. Zwei davon werden in Fachzeitschriften mit Peer-Review veröffentlicht und das dritte ist in Vorbereitung. Der Hintergrund, das Ziel der Studien, Ergebnisse, Diskussionen, allgemeine Schlussfolgerungen, Perspektiven und der experimentelle Teil werden in den Abschnitten 1-5 dargestellt.

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List of Publications

Publication 1

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

Kui Zeng, Jin Ye, Xintong Meng, Sebastian Dechert, Martin Simon, Shuaiyu Gong, Ricardo A. Mata, Kai Zhang*

Chem. Eur. J. **2022**, accepted. doi.org/10.1002/chem.202200648.

Publication 2

Direct Nitrogen Interception from Chitin/chitosan for the Preparation of Imidazo[1,5-*a*]pyridines

Kui Zeng, Ruhuai Mei, Xizhou Cecily Zhang, Loren B Andreas, Kai Zhang*

Chem. Commun. **2022**, 58, 6068-6071.

Publication 3

Anomeric Stereoauxiliary-organocatalyzed One-pot Site-selective C_2-aldehylation for Trisubstituted Indolizine-2-carbaldehydes

Kui Zeng, Jonathan J. Wong, Sebastian Dechert, Franc Meyer, K. N. Houk,* Kai Zhang*

In preparation **2022**.

Abbreviations and explanations

Ac	acetyl	HBTU	hexafluorophosphate benzotriazole tetramethyl uronium
Ac_2O	acetic anhydrate	HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
Alk	alkyl	HSQC	heteronuclear single quantum coherence
ADGF	2-acetamido-3,6-anhydro-2-deoxyglucofuranose	HRMS	high resolution mass spectrometry
[A]	amidation process	*J*	coupling constant
Ar	aryl	L	ligand
ADMF	2-acetamido-3,6-anhydro2-deoxymannofuranose	M	metal
3A5AF	3-acetamido-5-acetylfuran	Me	methyl
Bn	benzyl	*m*	*meta*
Bu	butyl	M.p.	melting point
BSA	*N*,*O*-bis(trimethylsilyl)acetamide	MHET	mono(2-hydroxyethyl) terephthalate
BH reaction	Baylis–Hillman reaction	NBS	*N*-bromosuccinimide
Boc	*tert*-butyloxycarbonyl	NCS	*N*-chlorosuccinimide
Cy	cyclohexyl	NBE-CO_2Me	2-carbomethoxynorbornene
CDC	cross-dehydrogenative coupling	NMR	nuclear magnetic resonance
Cis	functional groups (substituents) are on the same side of some plane	*o*	*ortho*
CmCDA	cyclobacterium marinum chitobiose deacetylase	[O]	oxidation process
DCE	1,2-dichloroethane	*p*	*para*
DMA	*N*,*N*-dimethylformamide	PA	propionic acid
DIEA	*N*,*N*-diisopropylethylamine	$Pd(dba)_2$	bis(dibenzylideneacetone)palladium
DMAP	4-(dimethylamino)pyridin	$PdCl_2(dtbpf)$	1,1′ -Bis-(di-tert.-butylphosphino-

			)ferrocen-palladiumdichlorid
DMSO	dimethylsulfoxide	Ph	phenyl
DNA	deoxyribonucleic acid	Piv	2,2-dimethylpropanoyl
DCAA	dichloroacetic acid	pKa	logarithmic acid dissociation constant
DFT	density funcational theory	Pr	propyl
DIBAH	diisobutylaluminum hydride	PET	poly(ethylene terephthalate)
EDG	electron-donating group	py	pyridine
EI	electron ionization	Pe	pentanyl
equiv.	equivalents	PMP	para-methoxyphenyl
E isomer	on opposite sides of the double bond	Pin	pinacol
ESI	electronspray ionization	δ	chemical shift
ee	enantiomeric excess	SET	single electron transfer
Et	ethyl	S_N1	first-order nucleophilic substitution
Enz	enzyme	S_N2	second-order nucleophilic substitution
EWG	electron-withdrawing group	*Si* face	originate from the Latin sinister (left)
FG	functional group	TMS	trimethylsilyl
FTIR	fourier transform infrared spectroscopy	*Trans*	functional groups (substituents) are on the opposing side of some plane
FAD	flavin adenine dinucleotide	TEA	triethylamine
FMF	5-(formyloxymethyl)furfural	*t*-Am	2-methylbut-2-yl
GlcN	D-glucosamine hydrochloride salt	TEMPO	2,2,6,6-tetramethylpiperidinyloxyl
GlcNAc	*N*-acetyl-D-glucosamine hydrochloride salt	Tf	trifluoromethanesulfonyl
GC-MS	gas chromatography-mass spectrometry	TFE	2,2,2,-trifluoroethanol
Hept	heptyl	THF	tetrahydrofuran
5HMF	5-hydroxymethylfurfural	TM	transition metal

HFIP	1,1,1,3,3,3-hexafluoro-2-propanol	*Tert*	tertiary

1. Introduction

Biomass is renewable organic material derived from plants, bacteria, fungi, protists, animals and viruses (**Figure 1**).[1] The biomass resource can be considered as organic matter in which solar energy is stored chemically.[2] In the past decade, research on biomass valorization has mainly focused on the (bio)chemical conversion of C-, H- and O-containing fractions (*viz.* DNA, RNA, carbohydrates, lignin, triglycerides and proteins),[2-18] whereas the *N*-containing fractions (*viz.* chitin, chitosan and D-glucosamine) have received little attention so far.[12,19,20] The abundant *N*-containing biomass, such as chitin and its derivatives, plays an irreplaceable role in organic organization.[18,21,22] In the following we will mainly discuss chitin and its derivatives.

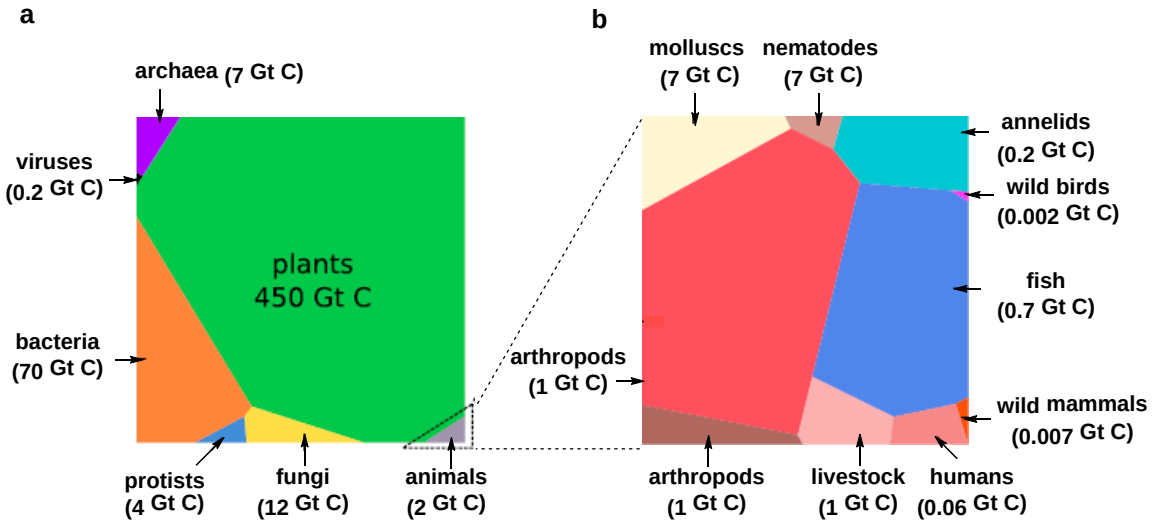


Figure 1 Graphical representation of the global biomass distribution by taxa: **(a)** Absolute biomasses of different taxa are represented using a Voronoi diagram, with the area of each cell being proportional to that taxa global biomass. Values are based on the estimates presented in ref.[1]. A visual depiction without components with very slow metabolic activity, such as plant stems and tree trunks, is shown in SI Appendix, Fig. S1 of ref.[1] **(b)** Absolute biomass of different animal taxa. Related groups such as vertebrates are located next to each other. We estimate that the contribution of reptiles and amphibians to the total animal biomass is negligible, as we discuss in the SI Appendix of ref.[1]. Visualization performed using the online tool at bionic-vis.biologie.uni-greifswald.de/. 1 Gt C = 1015 g of carbon. (Adapted with permission from ref.[1], Copyright from National Academy of Sciences.).

1.1 Chitin, chitosan and D-glucosamine

1.1.1 Origin, structures and characterization

Chitin, the second largest sustainable native polymer, can be found as a support material for many terrestrial organisms, marine organisms, microorganisms and crustacean shells (**Figure 2**).[18] For example, the organic matrice of honeybees is composed of 23%-32% chitin, 35%-45% proteins, 30%-40% melanin and 3% minerals.[23] Although chitin occurs in fungi, diatoms, nematodes, arthropods, and many other animals and plants, development has focused on extraction on a limited number of chitin species due to inconsistent physicochemical characteristics of products from aquatic organisms on an industrial scale.[24,25] Shrimps, crabs, lobsters, krill and squid waste from the marine processing industry has become a major resource in use today.[26]

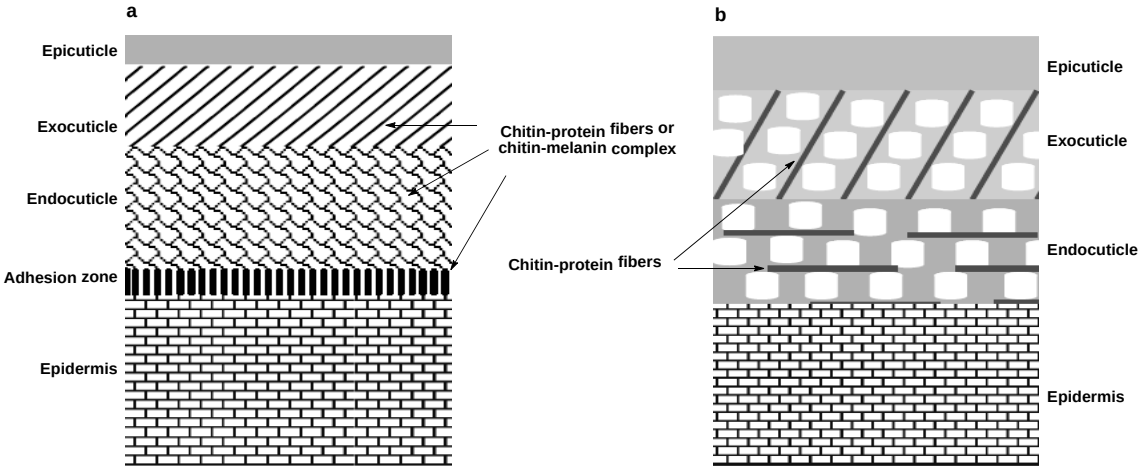


Figure 2 Schematic interpretation of organic matrix: **(a)** insect cuticle (rod and sheet types of chitin); **(b)** terrestrial crustacean (rod type of chitin) (Not drawn to scale. Adapted with permission from Ref.[18], Copyright from Taylor and Francis Group LLC (Books) US).

The main production processes for chitin and its derivatives are based on chemical,[27,28] enzymatic[29,30] and fermentative methods.[31-33] The general procedures for the extraction of chitin, chitosan and D-glucosamine from organic organisms include demineralization, deproteination, decolorization, deacetylation, hydrolysis and crystallization (**Figure 3**).[34-36]

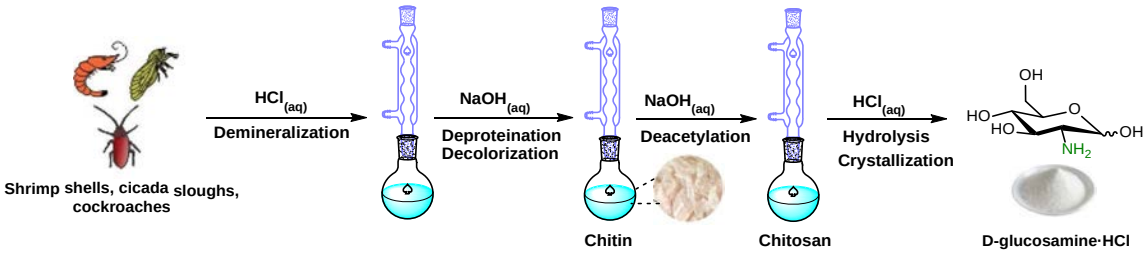


Figure 3 Schematic interpretation of the general procedure to obtain chitin, chitosan and D-glucosamine (Adapted with permission from Ref,[36] Copyright from WILEY-VCH Verlag GmbH & Co.).

Chitin is an abundant native linear copolymer composed of *N*-acetyl-D-glucosamine and D-glucosamine units linked with β-(1-4) glycosidic bonds (**Figure 4**).[18] Natural chitin samples may contain broadly different amounts of *N*-acetyl groups, depending on their origin and isolation procedure. The quantities of *N*-acetyl-D-glucosamine units are generally more than 50% in chitin backbone, while chitosan contains less than 50% *N*-acetyl-D-glucosamine.

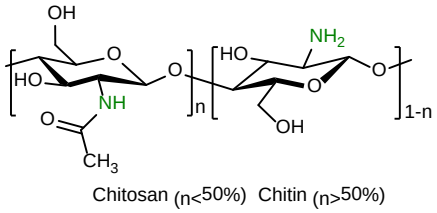


Figure 4 Schematic interpretation of chitin and chitosan structure.

Depending on the source, chitin in its natural state has three anhydrous crystalline polymorphs, including α-, β-, γ-chitin (**Table 1**).[37,38] β- and γ-chitin irreversibly convert to α-chitin, therefore, the α-chitin form is the majority of the three anhydrous crystalline polymorphs.[18] α-Chitin exhibits two antiparallel molecules per unit cell, while β-chiti n exhibits a parallel arrangement (**Figure 5**). α-Chitin has strong inter-sheet and intra-sheet hydrogen bonding.[39] β-Chitin has strong intermolecular hydrogen bonding (C=O and NH) between the chains along the a-axis[40] and weak hydrogen bonding by intra-sheets.[41] γ-Chitin has not been completely identified. Different from chitin as anhydrous crystalline polymorphs, chitosan is primarily a semicrystalline polymer in the solid state.[18]

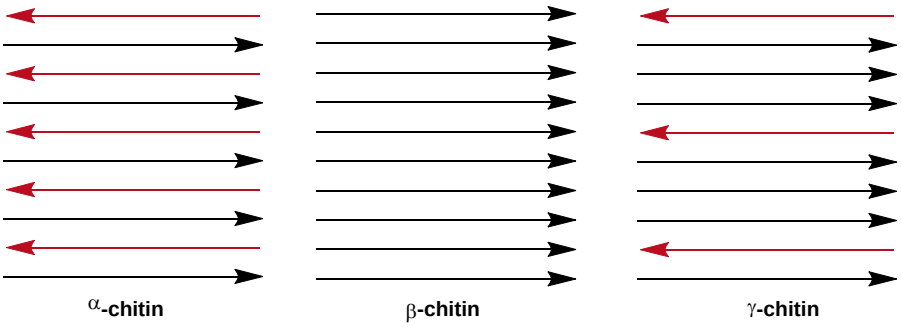


Figure 5 Antiparallel and parallel arrangements of different allomorphs of chitin.

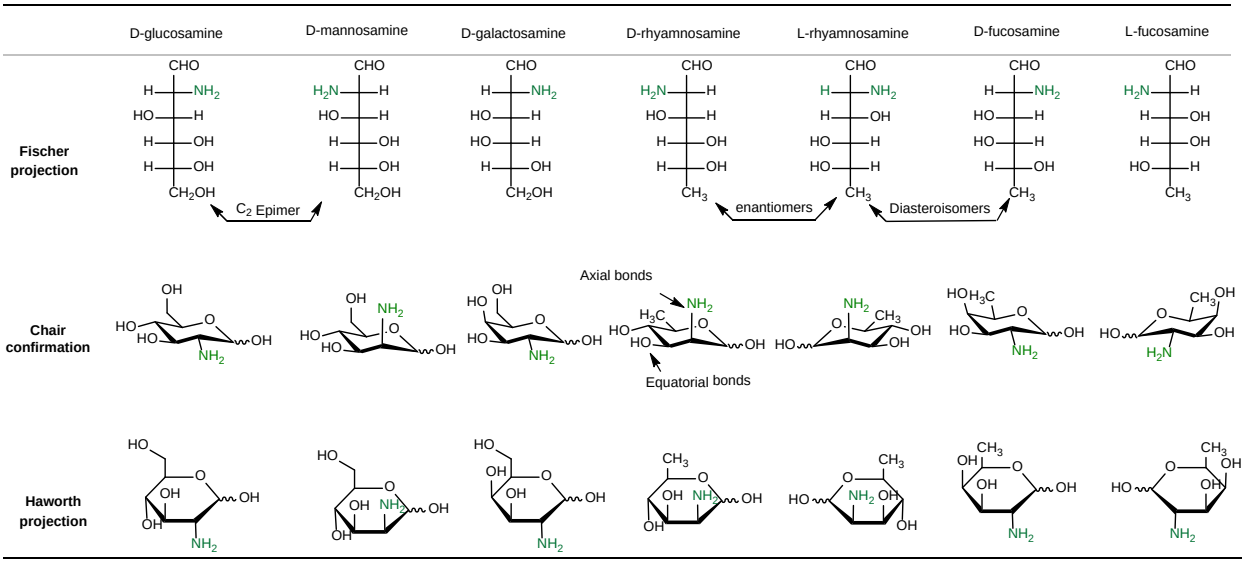
Table 1 Sources of chitin and chitosan

Types	Sources
α-chitin	Insects (cuticle,[42] ovipositors[43]); Crustaceans (Crab and shrimp shell); Centric Diatoms (Algae); Fungi (Mucor rouxi, Aspergillis nidulans[42])
β-chitin	Squid (Ommastrephes pen[44]); Centric Diatoms (Thalassiosira fluviatilis[45])
γ-chitin	Insects (Beetle cocoon[38]); Squid (Loligo stomach wall[46])

In amino sugars, the hydroxyl group of the sugar is replaced by an amino group. Theoretically any hydroxyl group of a sugar can be substituted. Therefore, there should be many different varieties of amino sugars. In nature, amino sugars are limited in number, including D-glucosamine, D-mannosamine, D-galactosamine, D/L-rhamnosamine, D/L-fucosamine and their *N*-acetyl derivatives (**Table 2**).[47] Sugar molecules with amino groups in unnatural positions can be artificially synthesiszed.[47]

D-glucosamine with four free hydroxyl groups and one free amino group is usually formulated as hydrochloride or glucosamine sulfate, which is hydrolyzed from chitin and chitosan. The hydroxyl group in the anomeric carbon C_1 of D-glucosamine contains α and β-anomer. Both forms are stable in the solid state, but interconvert in aqueous solutions to achieve equilibrium distributions through a mutarotation process (**Figure 6**).[36,48] The predominant anomeric form of unprotonated glucosamine is the β-form, while protonated glucosamine takes foremost the α-form.

Table 2 Representation of native amino sugars



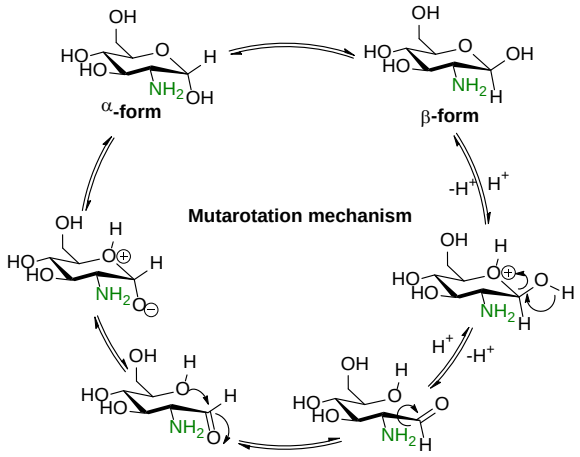


Figure 6 The mutarotation mechanism of D-glucosamine under aqueous conditions.[47]

1.1.2 Physical and chemical properties

Chitin as a highly crystalline material has specific solvent behavior, which is influenced by -NH_2 and -OH groups. Chitin is generally hydrophobic, soluble in hexafluoroisopropanol, chloroalcohols, and hexafluoroacetone mixed with an aqueous mineral acid solution, soluble in dimethylacetamide containing 5% lithium chloride, but insoluble in water and organic solvents at room temperature.[49] Due to the high degree of deacetylation, chitosan is generally dissolved in some organic acids (methanoic acid and acetic

acid *etc*.) and inorganic acids (1% hydrochloric acid, dilute nitric acid and lactic acid *etc*.) by protonation of amino groups. In contrast, chitosan is insoluble in alkaline and neutral aqueous solutions. The most frequently used solvent for chitosan is 1% acetic acid aqueous solution at pH 4.0. In addition, depolymerization of chitosan occurs at high temperatures in concentrated acetic acid.[50] D-glucosamine hydrochloride (GlcN) and *N*-acetyl-D-glucosamine hydrochloride (GlcNAc) are obtained by hydrolysis of chitin and chitosan. Generally, it is a white and sweet powder that decays at 221˚C.[51] The solubility of GlcNAc in water is about 25%. Chitin, chitosan and D-glucosamine have attracted great interest in developing diverse applications due to the beneficial properties such as excellent biocompatibility, antimicrobial activity and nontoxicity.[50-56]

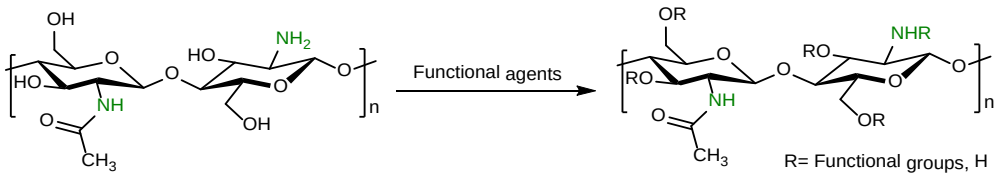
1.1.3 Modifications

Chitin, chitosan and D-glucosamine have natural active sites, including hydroxyl and amino groups, that can be easily further modified. The modified derivatives can show better solubility and interesting physicochemical properties for various applications.

There are many reviews on the modification of chitin and chitosan.[66,52] Therefore, we briefly summarize the four reaction types (**Table 3**). Sulfonation of chitin and chitosan is a general route to endow them with glycosaminoglycans-analogue biological activity.[52] In this respect, advances from diverse sulphating agents including H_2SO_4, SO_3, SO_3·pyridine complex, $ClSO_3H/H_2SO_4$, $ClSO_3H$/formic acid, $Me_3N{\cdot}SO_3$ complex, Oleum/DMF, $ClSO_3H$/formamide/dichloroacetic acid (DCAA) have widely expanded the chemical repertoire of accessible reaction sites (**Table 3**).[52,57,58] Phosphorylated chitin and chitosan have attracted considerable interest due to their anti-inflammatory properties, ability to form metal complexes, blood compatibility, and formation of anionic polyelectrolyte hydrogels. Therefore, tremendous synthetic strategies have been reported in the past decade. Representative phosphorylating agents are P_2O_5/CH_3SO_3H; H_3PO_4/urea; $H_3PO_4/P_2O_5/Et_3PO_4$; $ClP(O)(OEt)_2$; H_3PO_4/HCHO; $ClC_2H_4P(O)(OH)_2$; $PhP(O)(OH)_2$/HCHO (**Table 3**).[59-63] The most common method to increase the positive charge density of chitin and chitosan is to introduce quaternary ammonium salts (**Table 3**). The general direct method is a nucleophilic substitution reaction between the amino group of chitosan and an alkyl halide under alkaline conditions.[64,65] In another approach, the amino group of chitosan is first reacted with an aldehyde to form an imine, which is subsequently reduced by $NaBH_4$, and the reduced product is reacted with an haloalkane *via* a nucleophilic substitution reaction.[66,67] Indirect methods to introduce external quaternary ammonium groups broadly expand the types of reactants to include *N*-(3-chloro-2-hydroxypropyl) trimethyl ammonium chloride, glycidyltrimethyl ammonium chloride, (3-bromopropyl)

trimethylammonium bromide, (5-bromopentyl) trimethy-lammonium bromide *etc*.[68] The carboxyalkylation reaction of chitin and chitosan has attracted great attention in application fields such as biosensor wound healing, food industry, and bio-imaging.[69,70] To date, various synthetic agents have been explored, such as mono- or dicarboxylic acids (phthalic, succinic, maleic), acetic, propionic, butyric, valeric and hexanoic acids anhydride.[62,71-73] In addition to these four most prominent types of modification, there are several more interesting methods to mention here: thiolation, fluorination, *N*-pathaloylation and other cross-linking methods.[62]

Table 3. Modification of chitin and chitosan



Reaction types	Reaction agents	Ref.
Sulphonation	H_2SO_4; SO_3; SO_3·pyridine; $ClSO_3H/H_2SO_4$; $ClSO_3$/formic acid; $Me_3N{\cdot}SO_3$; Oleum/DMF; $ClSO_3H$/formanide/DCAA	52,57,58
Phosphorylation	P_2O_5/CH_3SO_3H; H_3PO_4/urea; $H_3PO_4/P_2O_5/Et_3PO_4$; $ClP(O)(OEt)_2$; H_3PO_4/HCHO; $ClC_2H_4P(O)(OH)_2$; $PhP(O)(OH)_2$/HCHO	59-63
Quaternary ammonium	Direct quaternization: Halogenated alkane; imine reduction; Indirect quaternization: Introduction of external quaternary ammonium groups *via* click reaction, nucleophilic substitution reaction	68
Carboxyalkylation	Mono- or dicarboxylic acids (phthalic, succinic, maleic), acetic, propionic, butanoic, valeric and hexanoic acids anhydride	62,71-73

D-glucosamine hydrochloride can generally be modified using organic synthesis strategies. There are many strategies for amino modification of D-glucosamine. The amino group of D-glucosmaine is easier to be modified than hydroxyl group due to their higher reactive activity. These mainly include Shiff's bases reaction (**Figure 7a**)[74-78] and amidation reaction (**Figure 7b**).[79-81] In 2019, Voglmeir *et al.* reported that the enzyme is capable of a series of *N*-acylation and *N*-transacylation reactions to prepare *N*-

acylglucosamines (**Figure 7c**).[82] This strategy overcomes the challenge of chemoselective acylation of glucosamine derivatives and is used for the total synthesis of sialosides.

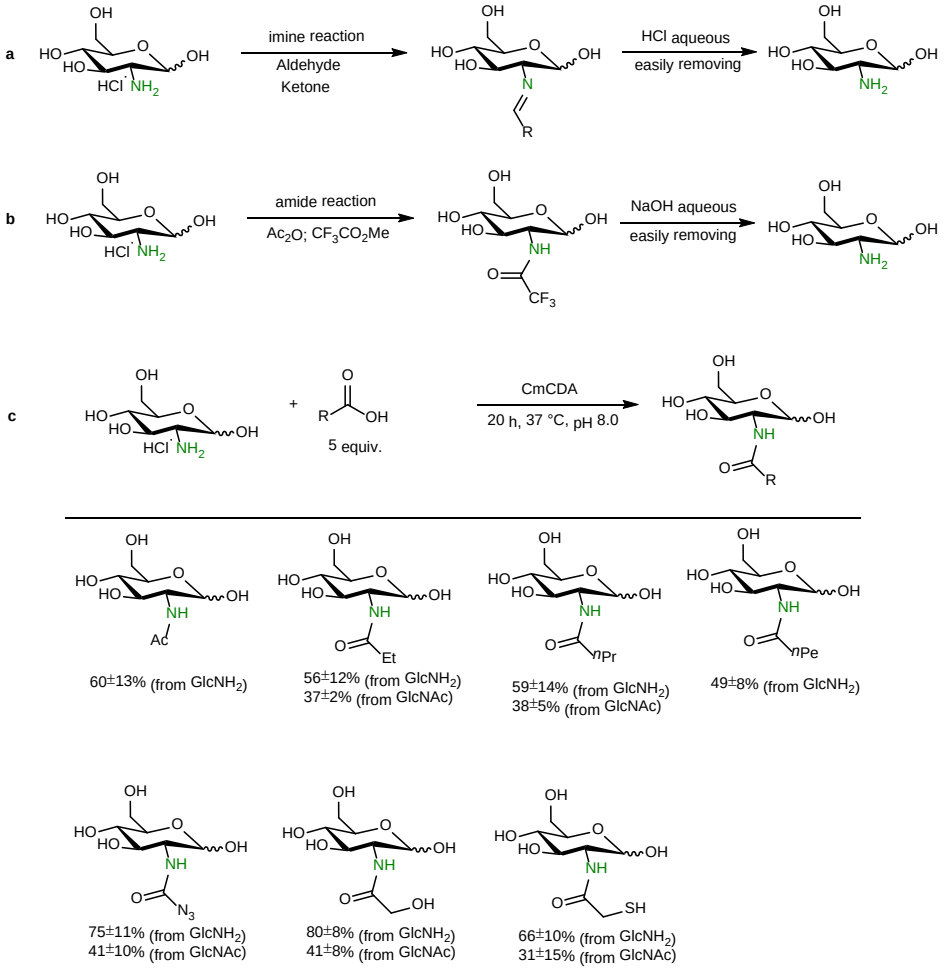


Figure 7 (a)-(b) The representative strategies of modifications of amino group of D-glucosamine. **(c)** Biocatalysis of D-glucosamine for *N*-acylglucosamines. CmCDA= Cyclobacterium marinum chitobiose deacetylase

Because these modified groups can be easily removed, for example, the imine group can be removed by hydrolysis with aqueous HCl (**Figure 7a**),[74-78] and the trifluoroacetyl group can be removed by hydrolysis with aqueous NaOH (**Figure 7b**)[79-81]. Therefore, chemists usually utilize them as representative block agents for site-selective modification of glucosamine. *O*-site-selective modification of glucosamine is possible by Shiff base reaction using aldehydes and ketones as block agent. The first imines derived from

2-amino-2-deoxyaldoses and salicylaldehyde were reported by Irvine and Hynd in 1913.[75,76] The method uses H_2O as the solvent and is limited to substrates with a hydroxyl group in ortho position. Costamagna *et al*. improved this strategy by using methanol as the solvent and applied it to the 2-hydroxynaphthylaldehyde substrate.[77] Nguyen *et al.* reported an efficent method for the preparation of imines *via* α-D-glucosamine and diverse aromatic aldehydes (**Figure 8a**).[78] After optimizing diverse base and solvent, NaOH and methanol are the best conditions. They discovered that those substrates with a hydroxyl group in the ortho position of the aromatic aldehyde gave more stable products. In 1950, Micheel and Wulff used unprotected glycosylazide with acetone to synthesize imines under acidic conditions. However, imines failed to obtain per-*O*-acetylated imines by the Ac_2O agent (**Figure 8b**).[83] Bertho, Wolfrom, Perez *et al.* reported and improved this reaction pathway from D-glucosamine in three steps (**Figure 8c**).[84-86] First, per-*O*-acetylated glycosylboro was synthesized with AcBr, and then the compound was further modified with AgN_3 to give per-*O*-acetylated glycosylazide. Finally, the desired imine product was obtained. Perez *et al.* also expanded the scope of ketone and stereochemistry by DFT and 2D-NMR analysis, providing more details.[85]

Per-*O*-acetylated *N*-TFA-glucosamine can be synthesized by amidation reaction using CF_3CO_2Me as a block agent and is widely used as a precursor of *O*-,[87,88] *S*-[89,90] and *N*-glycosides[91,92] (**Figure 9a**). For example, in 2004, Walsh *et al.* utilized this strategy to prepare glycopeptide variants of the antibiotic tyrocidine (**Figure 9b**).[91]

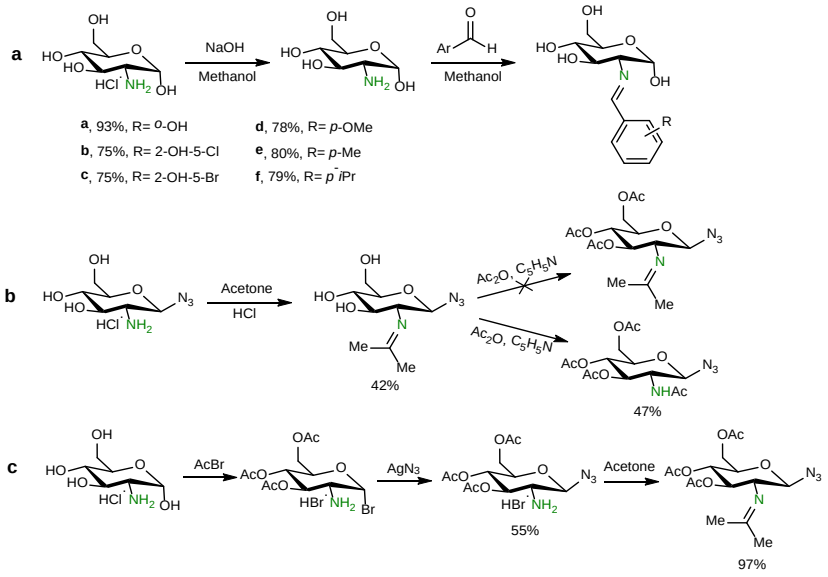


Figure 8 (a) Synthesis of imine *via* α-D-glucosamine with diverse aromatic aldehydes; **(b)**, **(c)** Synthesis of imine *via* D-glucosamine with ketone.

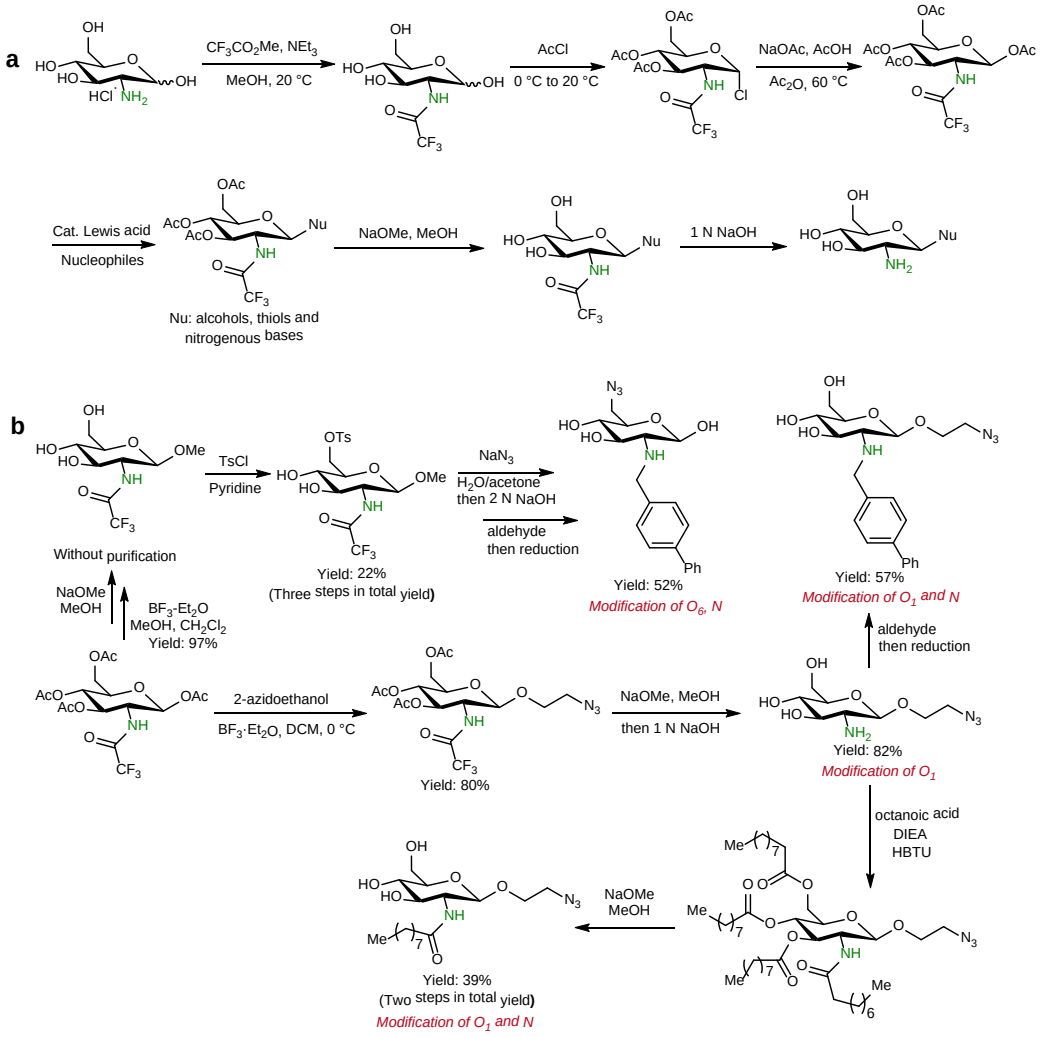


Figure 9 (a) Trifluoroacetyl as protected agents for diverse late-stage modifications. **(b)** one representative application example (here briefly show the synthesis parts of the ref.[88]). DIEA= *N*,*N*-Diisopropylethylamine. HBTU= hexafluorophosphate benzotriazole tetramethyl uronium.

1.1.4 Transformations

The transformation of chitin and chitosan reported in the literature mainly involves hydrolysis to produce monomeric $GlcNH_2$ and GlcNAc.[93-96] Here we do not mention the oligosaccharides of chitin and chitosan.[97,98] Monomers are further modified into value-added products, such as hydrogenation to prepare alcohols,[99-101] dehydration to synthesize nitrogen-containing-cyclic compounds,[102-113] oxidation to obtain carboxylic acid compounds,[114-116] dehydration-deamidation to prepare nitrogen-free aromatics,[117-121]

enzymatic/fermentative methods for the preparation of amino acid derivatives[13] and hydrogenation/ selective deoxygenation for the preparation of nitrogen-containing chemicals[122] (**Figure 10**). The mechanism of each type reaction was reviewed by Fukuoka *et al.*[12,123]

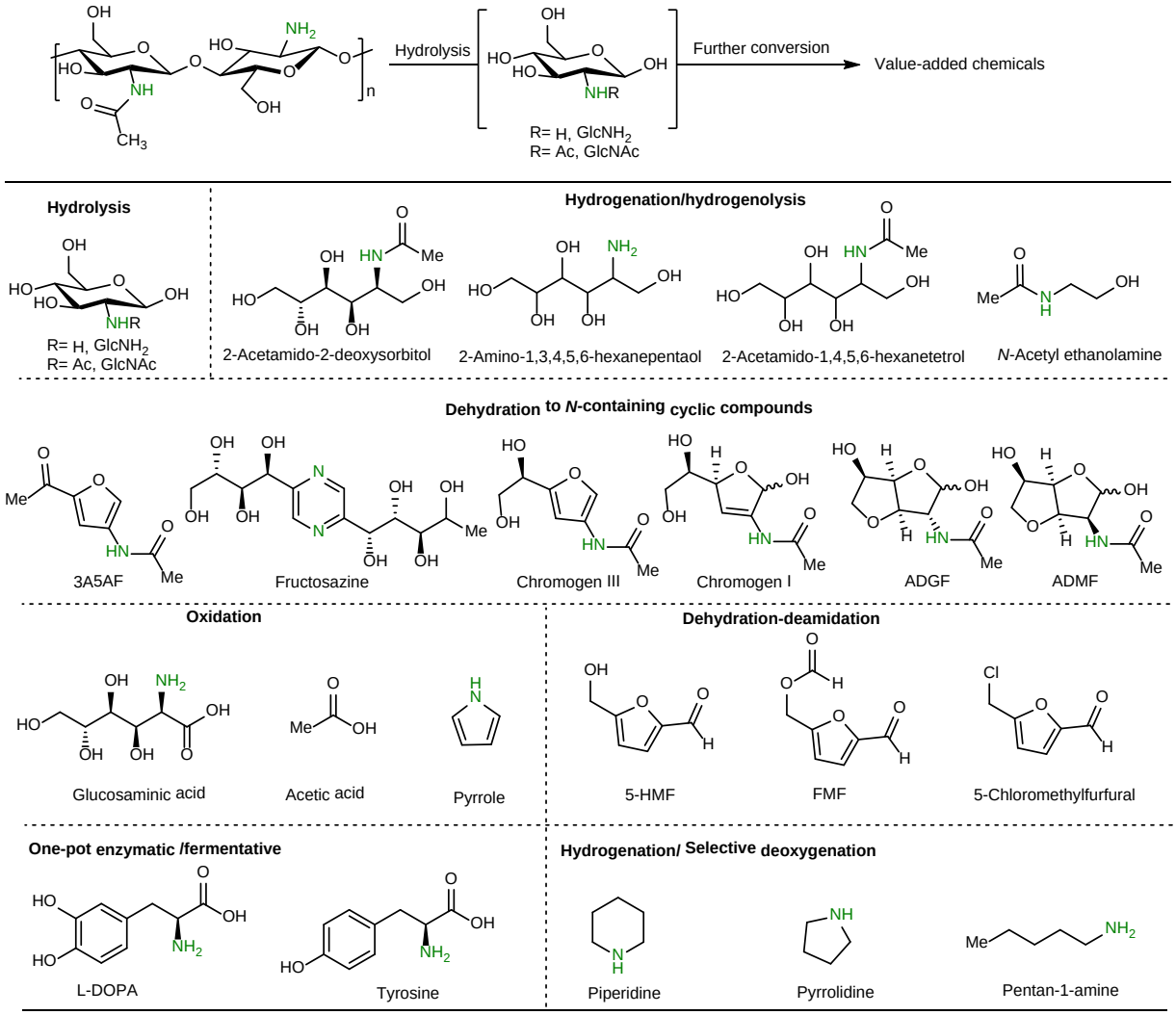


Figure 10 Synthesis of diverse value-added chemicals from chitin, chitosan and D-glucosamine. ADGF= 2-acetamido-3,6-anhydro-2-deoxyglucofuranose; ADMF= 2-acetamido-3,6-anhydro2-deoxymannofuranose; 3A5AF= 3-acetamido-5-acetylfuran; 5HMF= 5-Hydroxymethylfurfural; FMF= 5-(formyloxymethyl)furfural; L-DOPA= L-3,4-dihydroxyphenylalanine.

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 (**Figure 11**).[13] The process includes

pretreatment of chitin-containing shell waste and an enzymatic/fermentative bioprocess using metabolically engineered *Escherichia coli*.

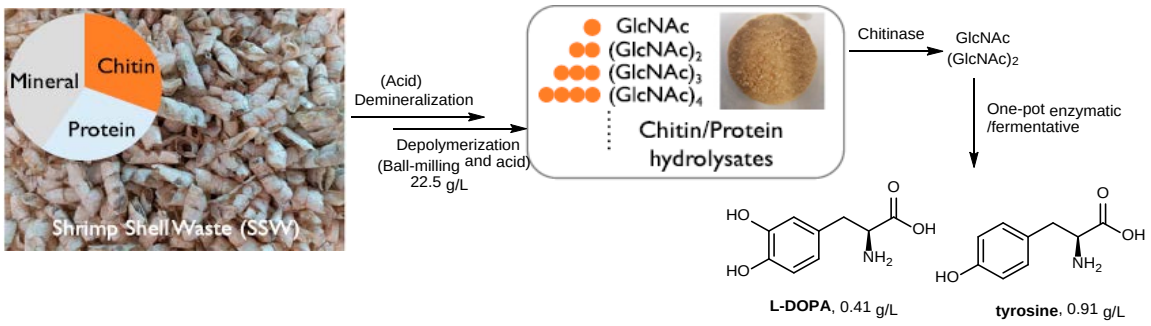


Figure 11 Synthesis of chiral aromatic amino acid from shrimp shell waste with biorefinery process. (Adapted with permission from Ref[13], Copyright from National Academy of Sciences.)

In 2021, Li *et al.* discovered an electrocatalytic method for the preparation of acetic acid and green hydrogen *via* chitin conversion (**Figure 12**).[116] Chitin was electrooxidized to acetate in hybrid electrolysis with yields exceeding 90%. This method also needs to obtain GlcNAc first, and then undergo glucosamine oxidation to acetic acid and H_2.

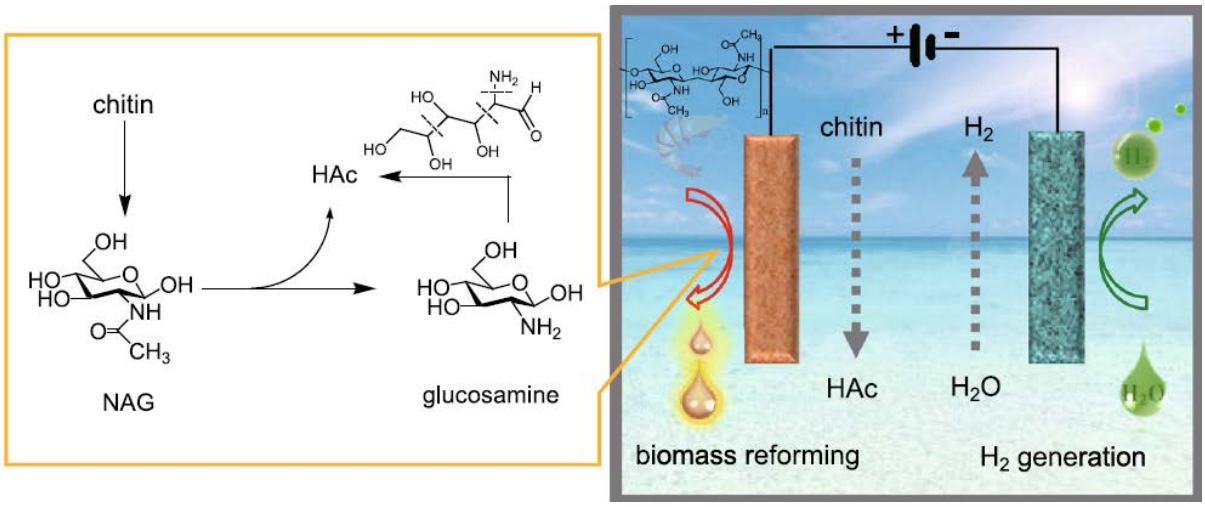


Figure 12 Synthesis of acetic acid from chitin with electrocatalysis. (Adapted with permission from Ref,[116] Copyright © 2021, The Author(s))

In 2021, Chen *et al.* reported the selective switchable conversion of chitin-derived *N*-actyl-D-glucosamine to organic acids at room temperature (**Figure 13**).[124] In this method, acetic acid and glyceric acid are obtained by using the oxidant O_2, and formic acid is obtained by using H_2O_2 as oxidant in the dilute NaOH solution. Compared with previous methods at high temperature and pressure, this method is economical, efficient and safety risks.

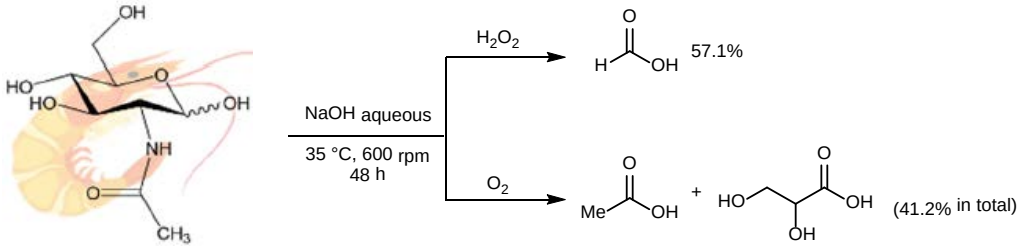


Figure 13 Selectivity-switchable conversion of *N*-actyl-D-glucosamine into commodity organic acids (Adapted with permission from Ref,[124] Copyright from 2021 American Chemical Society)

1.1.5 As ligands in organic synthesis

Enantiomerically pure compounds play important roles in pharmaceuticals, agrochemicals and flavors.[125,126] It can be obtained by organometallic, enzymatic and organocatalytic pathways. Among them, enantioselective homogeneous metal catalysis is an attractive strategy to obtain enantiomerically pure compounds. In 2001, W. S. Knowles, R. Noyori and K. B. Sharpless were awarded the Nobel Prize for their great achievements in this field.[127-129] In the process of catalytic enantioselectivity, ligands with stereostructures can cooperate with metal catalysts to form asymmetri chiral space. This facilitates the conversion of of prochiral substrates to chiral products. Therefore, the selection of suitable designed chiral ligands is the most critical step before the reaction. Until today, a series of ligands have been designed that greatly expand the scope of accessible structures and introduce their chiral properties into products.[130-133]

Carbohydrates are the most abundant and renewable biomass with a natural chiral backbone and are mainly used as carbohydrate-derived ligands for enantioselective reactions in organic synthesis.[134-136] It is shown to be economical and does not require pre-installation of chiral structures through multiple steps like artificial ligands. Many reviews cover ligand-derived sugar,[134-143] which are used as phosphine

ligands, phosphinite ligands, phosphite ligands for asymmetric hydrogenation, asymmetric hydroformylation, asymmetric allylic substitution, asymmetric 1,4-addition, asymmetric Heck reaction, asymmetric hydroboration, asymmetric hydrosilylation and asymmetric cyclopropanation. Here we mainly review chitin, chitosan and their monomers as ligand precursors in organic synthesis (**Figure 14**).

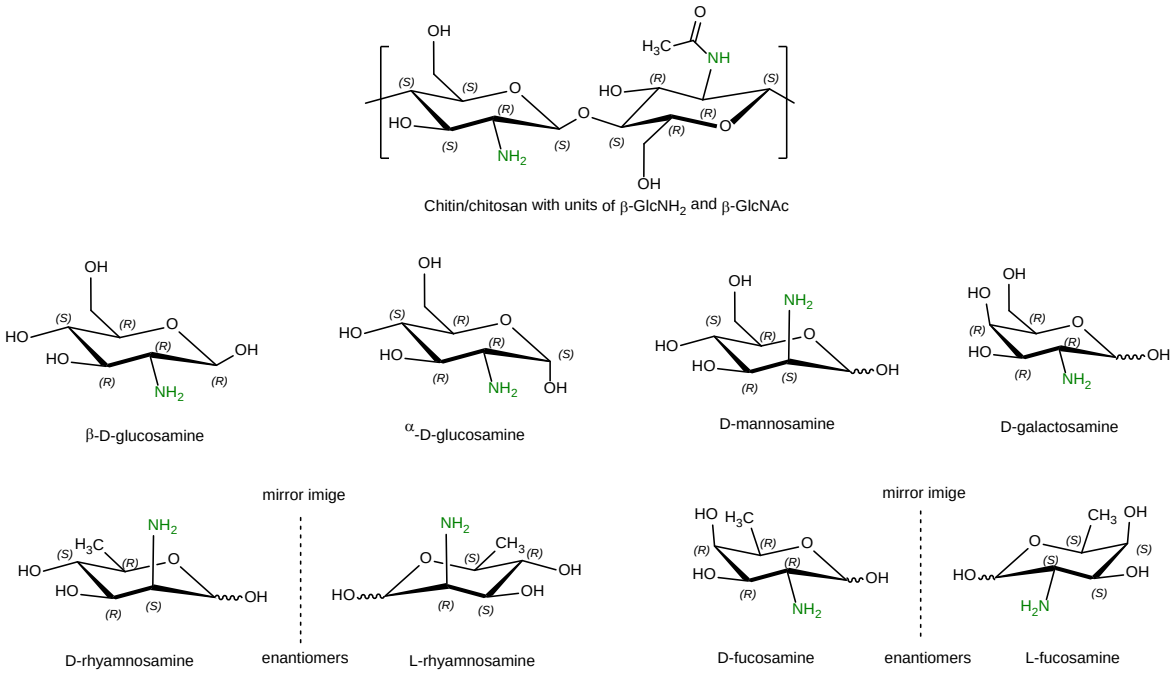


Figure 14 Stereochemistry of native chitin, chitosan and amino sugars.

The natural chitin, chitosan, and amino sugars with amino groups endow them higher reactive activity than those carbohydrates without amino groups. *N*-containing carbohydrates can be easily modified to desired ligands to improve its reactivity in organic synthesis applications (**Figure 15a**).[144,145] Kunz *et al.* in 1998, first time utilized D-glucosamine for phosphine oxazoline (phox) ligand.[146] Uemura *et al.* improved this ligand with a diphenyl phosphinite group for asymmetric allylic substitution reactions.[147,148] Ligand $\mathbf{L_5}$ is used as a phosphinite-oxazoline ligand for the asymmetric Heck reaction and for the enantioselective arylation of 2,3-dihydrofuran with aryl triflate (**Figure 15b**).[149] Boysen *et al.* introduced a C_2-symmetrical bis-(oxazoline) ligand $\mathbf{L_7}$ derived from D-glucosamine. This ligand is used for copper-catalyzed cyclopropanations of styrene with diazoacetate (**Figure 15d**).[150] The ligand $\mathbf{L_8}$ designed by Bauer *et al.* was used to the addition of diethylzinc to aldehydes with high enantiomeric excess (*ee*) and yield (**Figure 15e**).[151] In 2005, Dieguez *et al.* designed and synthesized a new family of readily available

phosphite-oxazoline ligands **L_6** for Pd-catalyzed asymmetric allylic substitution reactions (**Figure 15c**).[152] In 2006, a group of amino sugars (**L_1-L_4**) were usesd as chiral ligand additives for the addition of diethyl zinc to aldehydes (**Figure 15f**).[153] Both **L_1** with the α-anomer and **L_2** with the β-anomer can achieve excellent yields and *ee*. However, low yields and *ee* can be achieved with α-allosamine **(L_3)**, while high yields with low ee can be achieved with α-mannosamine (**L_4**). It was concluded that the α/β anomers do not affect the yield and *ee* of these reactions. The hydroxyl group on C_3 plays an important role in the yield of the reaction, while the amino group on C_2 helps to control the *ee*. Based on these results, they proposed a mechanism for the formation of a five-membered ring between the hydroxyl group on C_2, amino group and zinc.

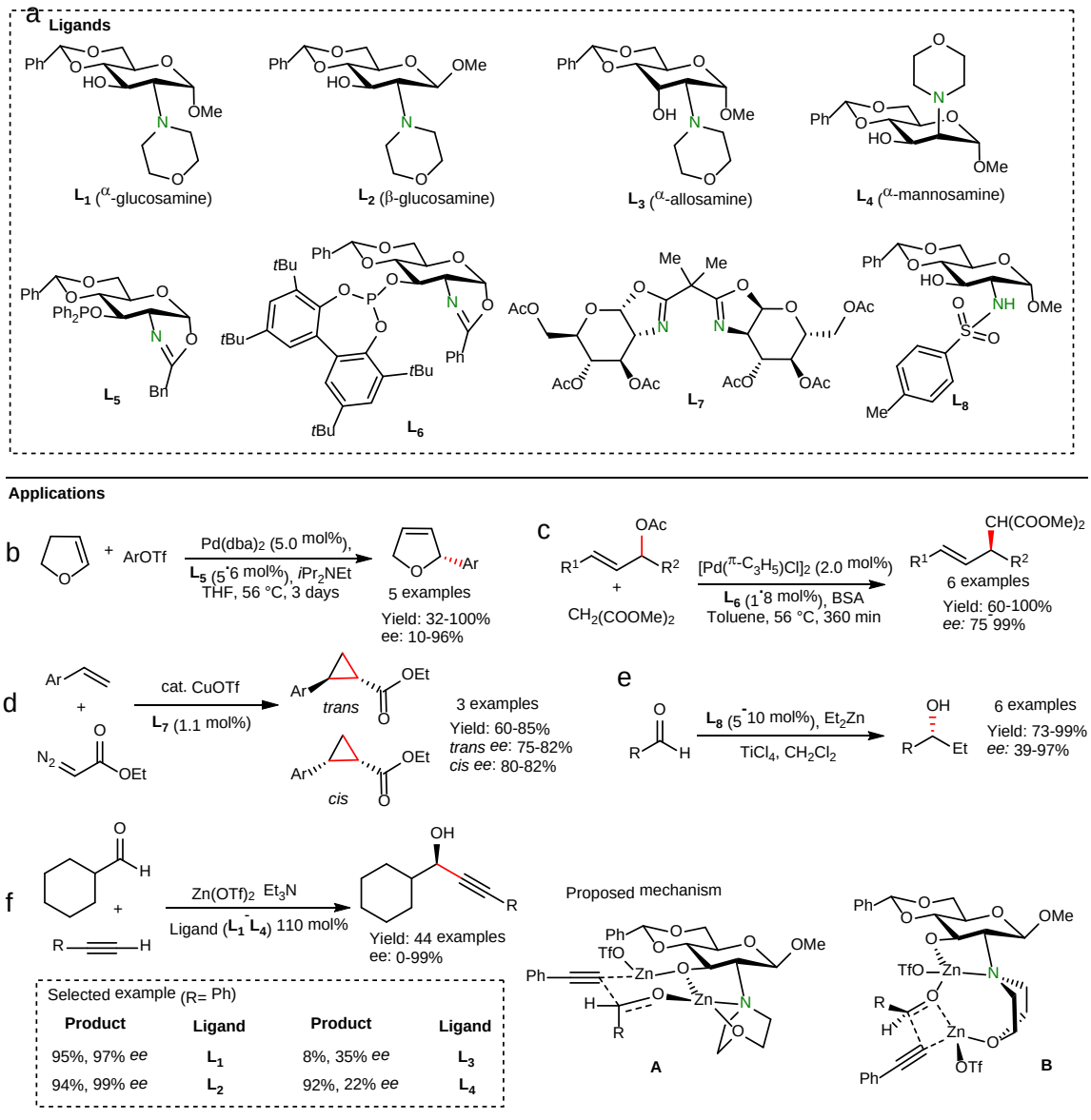


Figure 15 Representatives examples of ligands derived amino sugar and their applications. $Pd(dba)_2$= Bis(dibenzylideneacetone)palladium; BSA= *N*,*O*-bis(trimethylsilyl)acetamide; *ee*= enantiomeric excess.

In addition to asymmetric catalytic organic synthesis, in 2008, Bao *et al.* reported D-glucosamine as a ligand for the Ullmann reaction-type *N*-arylation of imidazoles with aryl and heteroaryl bromides (**Figure 16a**).[154] In 2016, Zhou *et al.* not only improved this reaction not only in an air atmosphere by utilizing GlcNAc, but also expanded the substrates from imidazoles to aromatic amines (**Figure 16b**).[155] The role of GlcNAc was demonstrated by theoretical studies, suggesting that the hydroxyl groups at C_3, C_4, and C_6 positions may have a significant influence on the catalytic process. However, the role of the hydroxyl group on C_1 and the role of the amino group on C_2 have not been investigated. In 2011, Sekar *et al.* reported D-glucosamine as an efficient ligand for the copper-catalyzed selective synthesis of anilines from aryl halides and NaN_3 (**Figure 16c**).[156] In 2014, Zhang *et al.* discovered D-glucosamine used as a ligand for copper-catalysed synthesis of aryl sulfones from aryl halides and sodium sulfonates (**Figure 16d**).[157] Zhang *et al.* extended the strategy for the cross-coupling reaction of diphenyl disulfides and aryl iodides in the presence of CuI and glucosamine (**Figure 16e**).[158] D-glucsaomine has also been used in the palladium-catalyzed Mizoroki-Heck reaction of aryl hades (**Figure 16f**)[159] and the iron-catalyzed Grignard cross-coupling reaction of vinylic and allylic bromides (**Figure 16g**).[160]

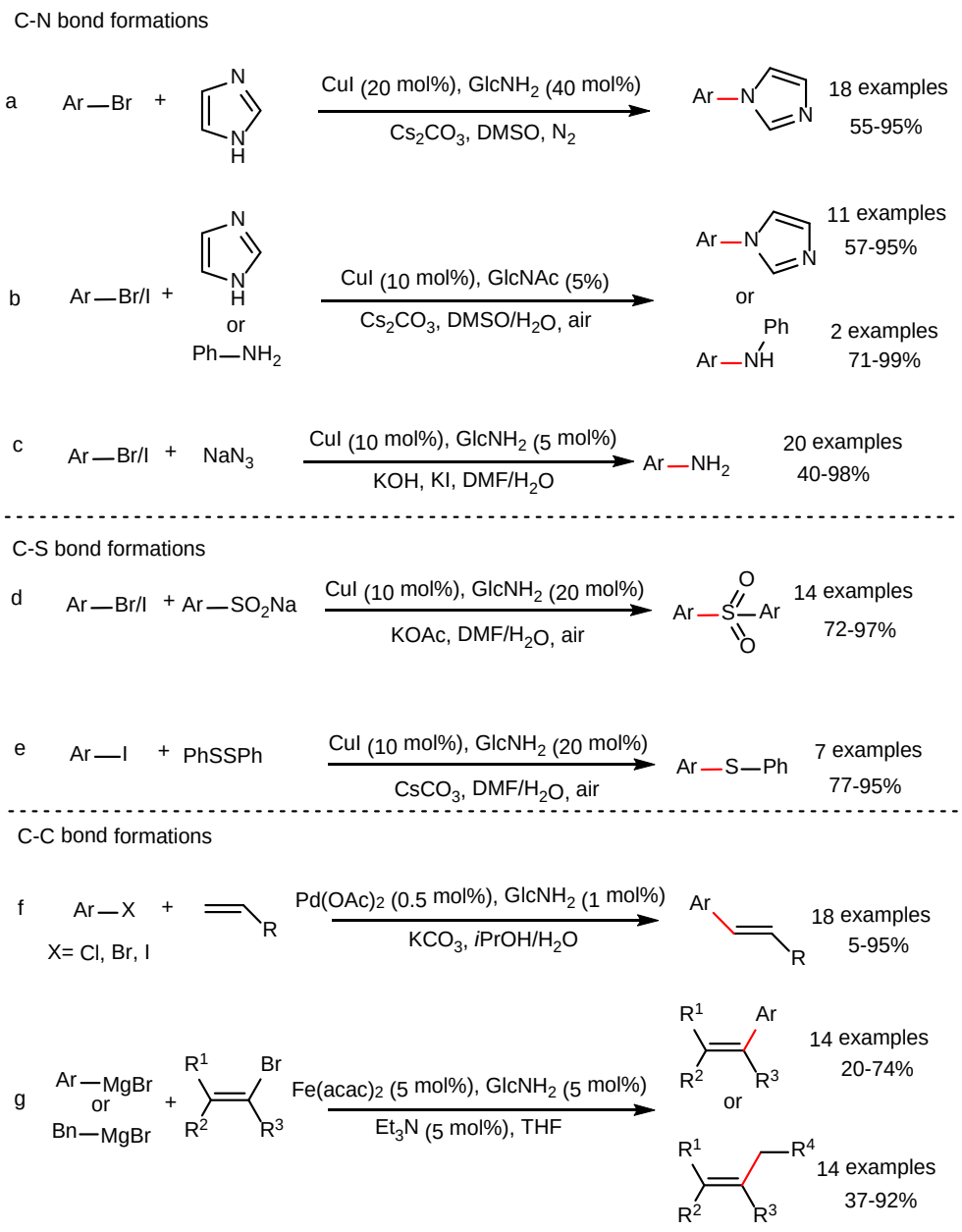


Figure 16 Construction of C−N, C−S and C−C bonds *via* the metal-catalyzed with ligand D-glucosamine. $Fe(acac)_2$= iron(II) acetylacetonate.

1.1.6 As organocatalysts in organic synthesis

Organocatalysis is one of the most thriving research fields in contemporary organic synthesis.[161-166] A variety of classical organocatalyst types have been reported, which highly expand their range of applications from value-added fine chemical production to natural product synthesis and drug discovery.[166-177] Since the chiral backbone of aminocatalysts has tunable steroauxiliary groups, which help to form strong steric shielding, in 2000, Benjamin list *et al.* first reported the use of proline as a catalyst to direct realize asymmetric aldol reactions through enamine process.[178] In the same year, David W. C. Macmillan *et al.* first demonstrated the highly enantioselective organocatalytic Diels-Alder reaction through the iminium-catalyzed pathway.[179] Benjamin list and David W. C. Macmillan were awarded Nobel Prize in 2021. Until today, iminium and enamine catalysis methods based on covalent mechanisms has drawn much attention.[180-186] Despite the enormous advance in these aminocatalysts modes, a sustainable and cheaper organocatalyst with natural chiral skeleton derived from biomass for the enantiselective synthesis are still highly desirable.

In 2007, inspired by bifunctional urea Schiff base organocatalysts,[187,188] the first example of a highly efficient organocatalyst for enantioselective Strecker and Mannich reactions was constructed from glucosamine as a readily available chiral scaffold (**Figure 17b**).[189] In the Strecker reaction, catalyst **Cat$_1$** shows an excellent 95% *ee*, while catalyst **Cat$_2$** only achieves 15% *ee*. Compared with the Strecker reaction, the catalyst **Cat$_1$** exhibited poor *ee* in the Mannich reaction (**Figure 17c**). In 2012, Miao *et al.* developed sugar-derived thiourea organocatalyst for the catalytic asymmetric addition reaction of α-ketophosphonates and TMSCN with excellent *ee* and high yield (**Figure 17d**).[190-192]

In 2006, Wong *et al.* demonstrated that the sugar moiety of a glycopeptide modified with a thiol handle at the C_2 position can facilitate the ligation of cysteine-free glycopeptided to thioester peptide (**Figure 18**).[193-200] In this work, they propose that the sugar moiety affects the proximity of the *N*-terminal amine to the thioester. This provides acyl transfer to obtain the final product. But they did not explain the configuration of the anomertic center and the *N*-linked sugars, their effect on the fate of ligation. Two years later, they expanded the sugar types with more elaborate sugars for glycopeptide ligation.[194] In 2016, Liu *et al.* reported a practical approach for the synthesis of *N*-glycopeptide using an auxiliary-mediated dual native chemical ligation.[201]

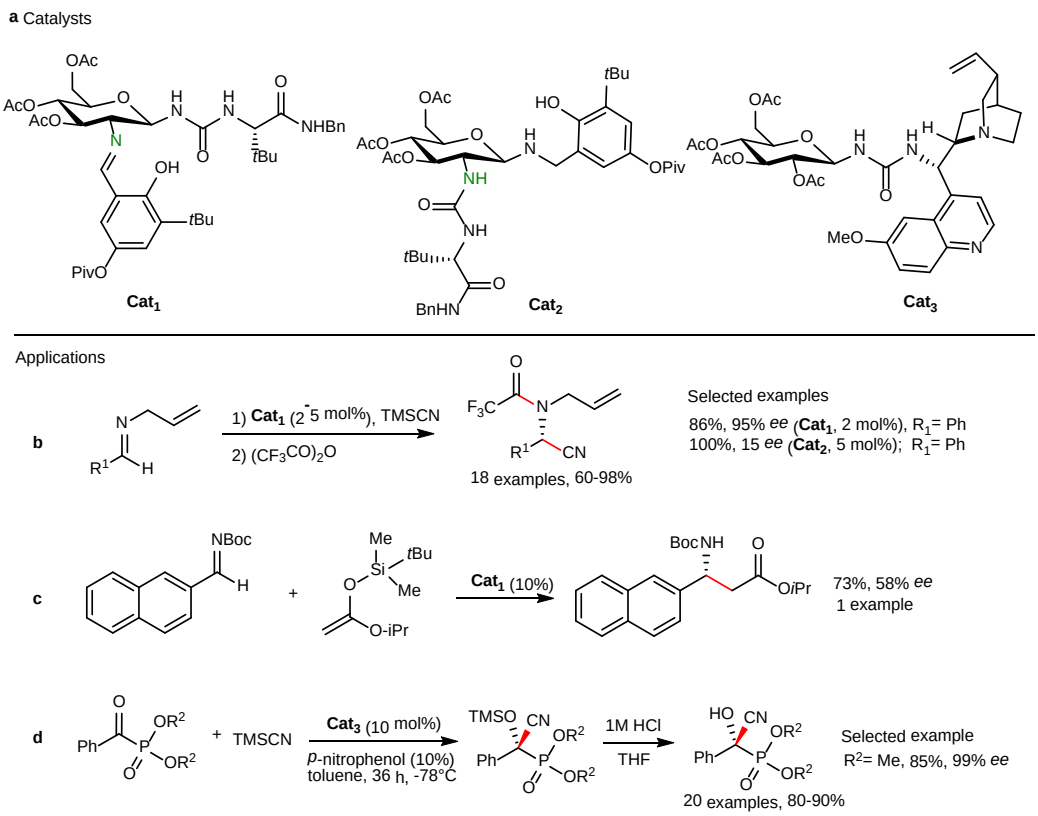


Figure 17 The sugar-derived thiourea organocatalysis and applications.

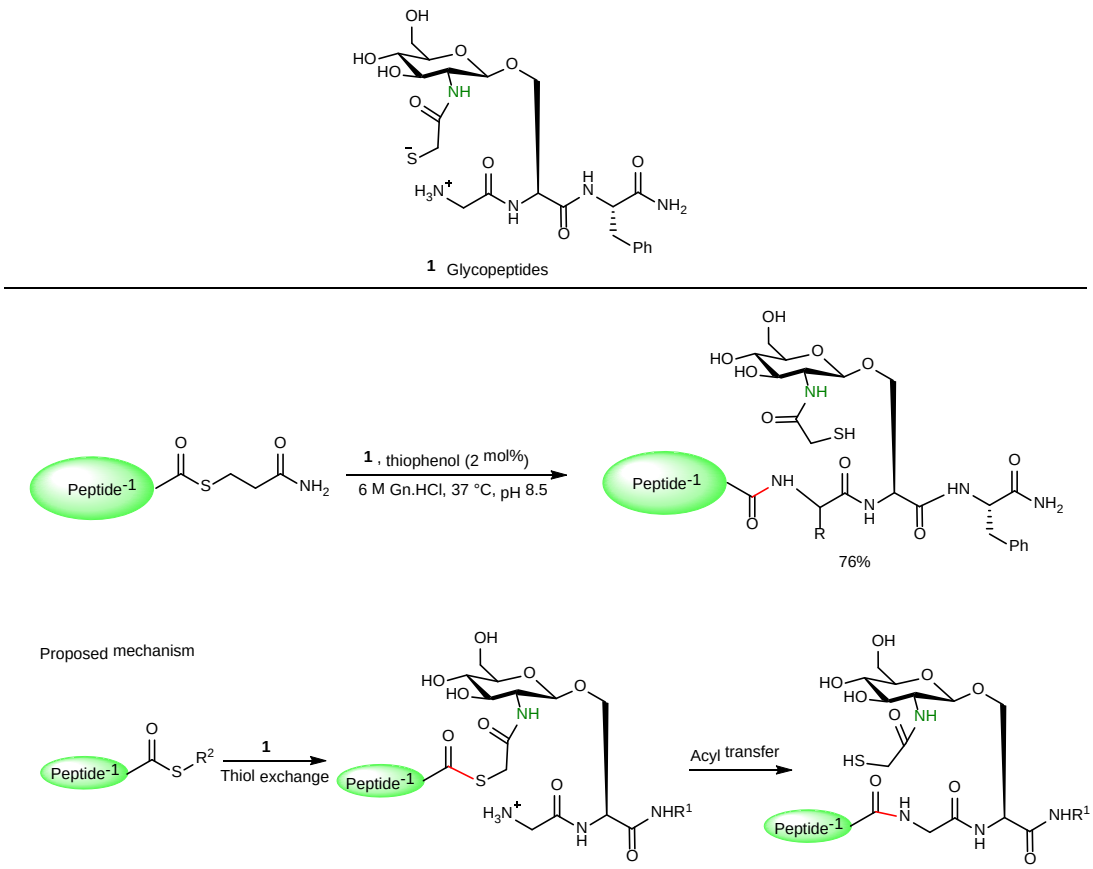


Figure 18 Sugar-assisted glycopeptide ligation.

2. Objectives

1) Targeted cleavage of the C−N bond of D-glucosamine *via* a metal-free pathway and the conjunction of nitrogen in the synthesis of imidazo[1,5-a]pyridines remains a great challenge. Despite tremendous progress in the synthesis of imidazo[1,5-a]pyridines over the past decade, many of them still cannot be efficiently prepared. Therefore, an novel anomeric stereoauxiliary approach for the synthesis of a wide range of imidazo[1,5-a]pyridines after cleavage of the C−N bond of D-glucosamine (α-2° amine) from biobased sources is highly desirable (**Figure 19**).

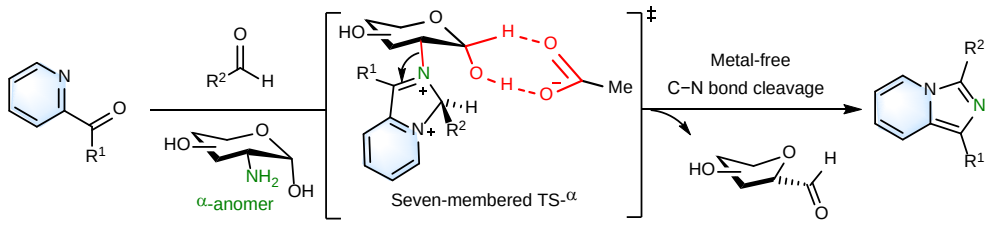


Figure 19 Anomeric stereoauxiliary strategy enables efficient synthesis of wide-ranging imidazo[1,5-a]pyridines.

2) Nitrogen-containing chemicals (NCCs) play a pivotal role in modern life, but direct nitrogen interception from the renewable nitrogen-containing polysaccharide chitosan/chitin for synthesizing value-added NCCs is still a big challenge. Herein, a facile and efficient one-pot methodology that enables direct nitrogen interception of chitosan/chitin for the synthesis of a broad range of important *N*-heterocycles imidazo[1,5-a]pyridines are highly attractive (**Figure 20**).

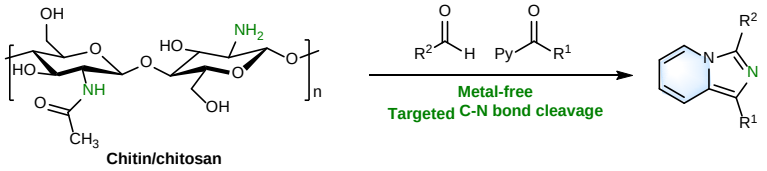


Figure 20 Simultaneous C-N cleavage and incorporation of nitrogen from chitin/chitosan for imidazo[1,5-a]pyridines.

3) Today, there are still no examples of glucosamine being used only as aminocatalysis. Therefore, sustainable aminocatalysts with native chiral skeletons derived from *N*-containing biomass for the regioselective cyclization are highly attractive, but not yet realized. On the other hand, indolizine-carbaldehyde is an important synthetic target. The easily modified carbaldehyde group makes them versatile precursors for diverse indolizines. However, the chemical construction of trisubstituted indolizine-2-carbaldehydes with efficient one-pot direct site-selective C_2-aldehylation represents a long-standing challenge for synthetic chemists.[202,203] Herein, a novel anomeric stereoauxiliary aminocatalysis approach is highly desirable for the efficient one-pot preparation of trisubstituted indolizine-2-carbaldehydes with highly site-selective C_2-aldehylation *via* dehydration [3+2] annulations (**Figure 21**).

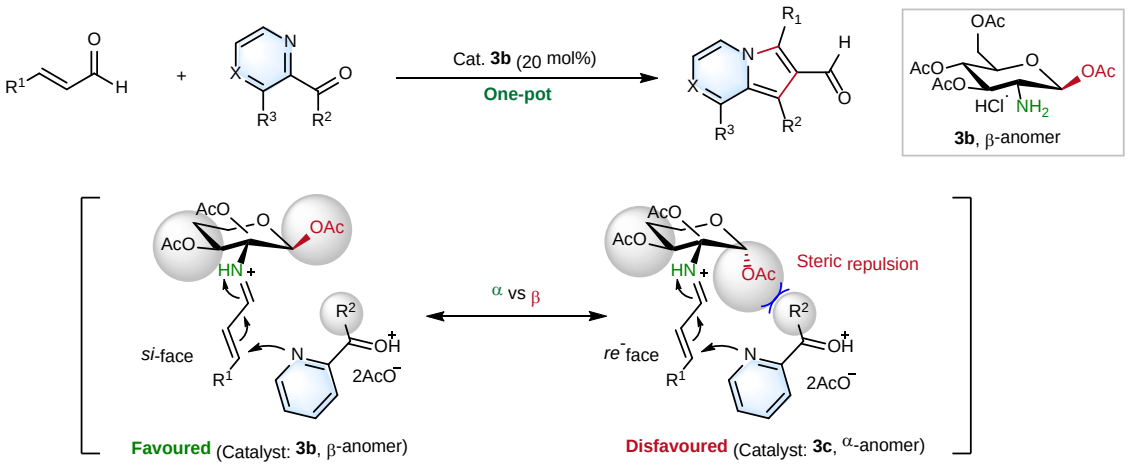


Figure 21 Anomeric stereoauxiliary-organocatalyzed one-pot site-selective C_2-aldehylation for trisubstituted indolizine-2-carbaldehydes.

3. Results and Discussion

3.1 Publication 1: Anomeric Stereoauxiliary Cleavage of the C−N Bond of D-glucosamine for the Preparation of Imidazo[1,5-a]pyridines

3.1.1 Background

The C−N bonds are ubiquitous in many biobased organic molecules, especially in many biomolecules of living organisms.[204-206] The utilization and transformation of C−N bonds are among the central topics in organic chemistry, biochemistry and material science,[207-210] while only a few examples of the C−N cleavage of alkyl primary amines were reported recently with the assistance of metal-catalysts. Up to now, most protocols are limited to primary amines with benzylic, allylic and pyridine.[210-215] It is still highly attractive to develop efficient strategies for selective C−N bonds 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 *via* single electron transfer to Katritzky pyridinium salts intermediates (**Figure 22a**).[216-219] Later in 2020, the Rovis group demonstrated a visible light photoredox approach to cleave C−N bonds of α-3° primary alkyl amines *via* a key imidoyl radical intermediate (**Figure 22a**).[220] Moreover, the Milstein group reported a catalytic oxidative deamination protocol with ruthenium pincer complex (**Figure 22a**).[221] Until now, all the reported methods for C−N bonds cleavage in alkyl primary amines require transition metal catalysts. Unlike these previous strategies towards the cleavage of C−N bond via metal catalysts, we present here a metal-free anomeric stereoauxiliary strategy to cleave the C−N bond of native D-glucosamine (α-2° amine) from biobased resources, which offers a readily accessible and sustainable route for the synthesis of a broad range of imidazo[1,5-a]pyridines (**Figure 22b**).

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.[222-229] For example, they can be precursors of *N*-heterocyclic carbenes,[222-224] ligands in coordination chemistry,[225,226] and inhibitors of biologically active agents.[227-229] 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,[230] imidazo[1,5-a]pyridines are attractive optical materials for many applications[231-233]. 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.[234] This method was continually improved and widely used in synthetic chemistry and for optical materials,[235] 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 *via* transannulation of pyridotriazoles process.[236] 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.[237] Although this strategy widely expanded the library of accessible structures, the study showed only 6 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.[238,239239] The challenges in accessing 1-alkylimidazo[1,5-a]pyridines *via* 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.[238] 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 side-reaction.[240] Therefore, it is highly desired to develop a strategy to overcome these disadvantages.

Carbohydrates as chiral auxiliaries in stereoselective synthesis[134,241] and stereochemistry of transition metal complexes controlled by the metallo-anomeric effect[242] 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.[36,48] 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.

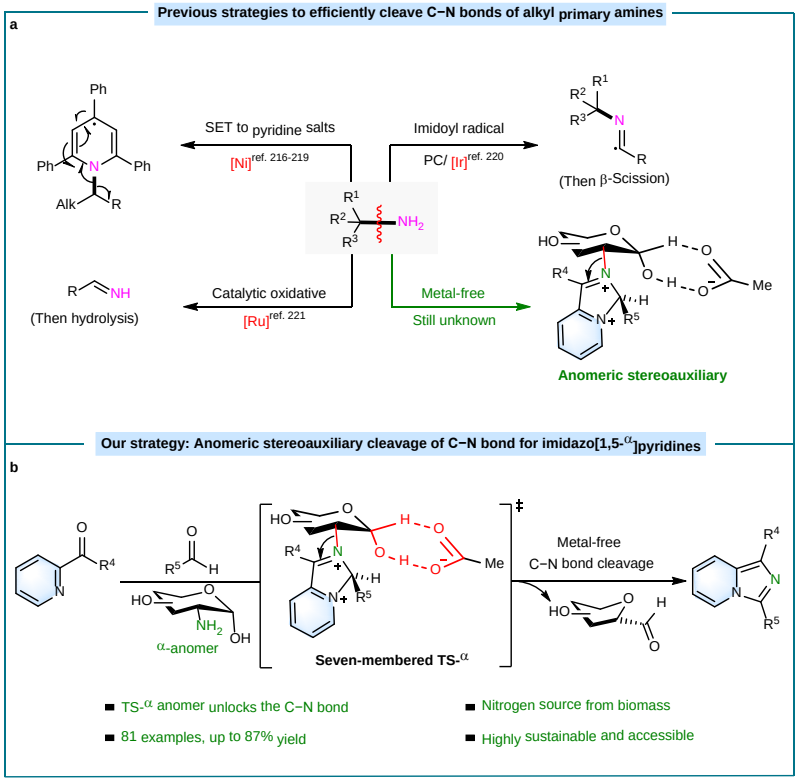


Figure 22 (a) The representative example of previous strategies for the cleavage of the C−N bonds of alkyl primary amines. **(b)** Our strategy: cleavage of C−N bond for imidazo[1,5-a]pyridines via anomeric stereoauxiliary.

3.1.2 Optimization studies

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** of **Publication 1**). After extensive experimentation, we got the optimal condition for the efficient synthesis of imidazo[1,5-a]pyridines with 74% yield using D-glucosamine as nitrogen source in a solvent mixture (v_{AcOH}:v_{H2O} of 9:1) at 120 ˚C under Ar gas atmosphere (**Figure 23a**). In parallel, commercial acetylated amine sugars as stabilized α-anomer (**3b**) and β-anomer (**3c**) were used for the reaction under the optimal conditions (**Figure 23a**). 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 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 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 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 pKa, solvent mixtures with various pK_a (0.9 mL) and H_2O (0.1 mL) were investigated under optimal conditions (**Figure 23b**). 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-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.[243]

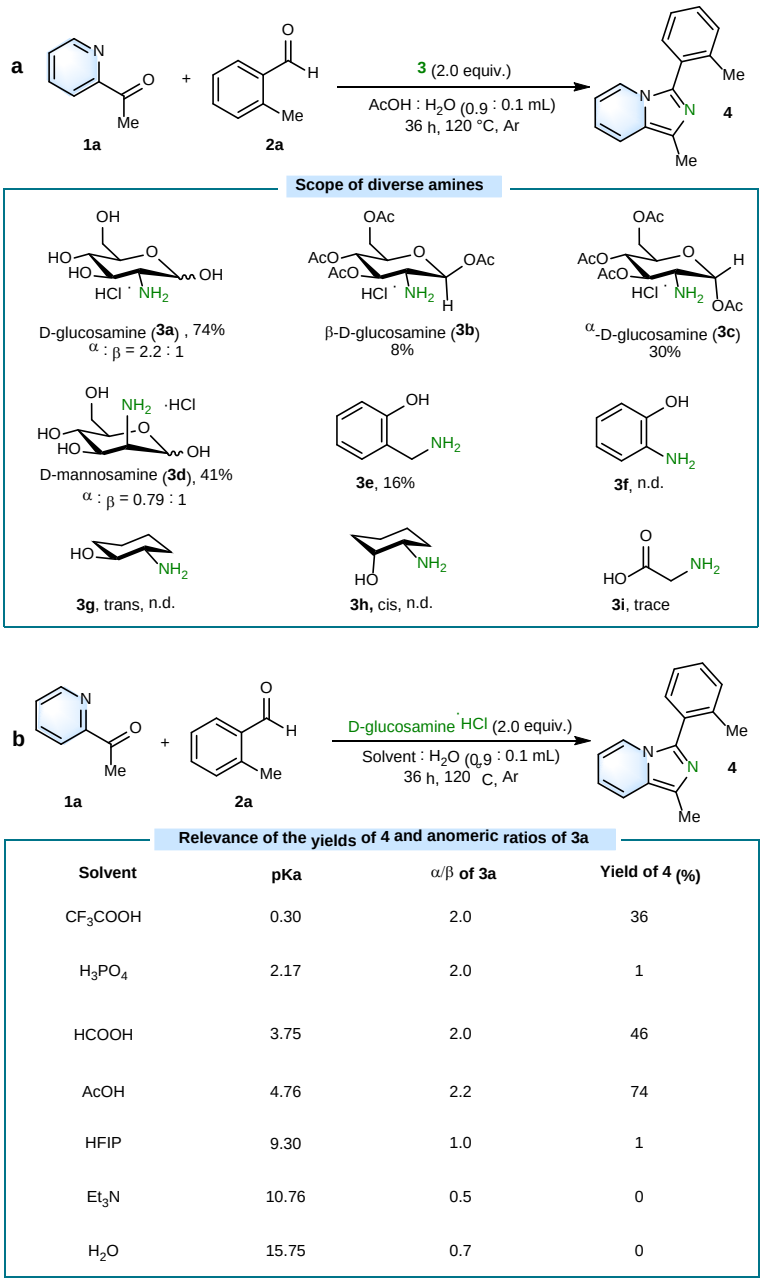


Figure 23 Reaction development. **(a)** Diverse amino compounds **3a-3i** were used in reactions in the solvent mixtures (vAcOH:vH_2O of 9:1) at 120 ˚C under Ar gas atmosphere. **(b)** Various mixtures of solvents with various pK_a (0.9 mL) and H_2O (0.1 mL) were used for the reactions under the optimal conditions. pK_a of CF_3COOH,[244] H_3PO_4,[245] HCOOH,[246] CH_3COOH,[247] 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),[248] Et_3N,[249] and H_2O[250] are 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_2Br_2 as the internal standard.

3.1.3 Scope of substrates

With the optimized reaction conditions in hand, we next probed the scope of various aldehydes using 2-acetypyridine as a representative heteroaryl ketone (**Figure 24**). 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 (product **27**-**28**) were also well compatible with this approach. Furthermore, a series of aliphatic aldehydes, including cyclic aldehydes (product **29**-**30**) and aldehydes with aliphatic chains (product **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 (**Figure 25**). 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 corresponding products **37**-**43**. The functional groups at diverse positions, such as methyl (**38**-**39**), methoxyl (**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 properties. The structure of **51** was further assigned with X-ray crystallographic analysis.

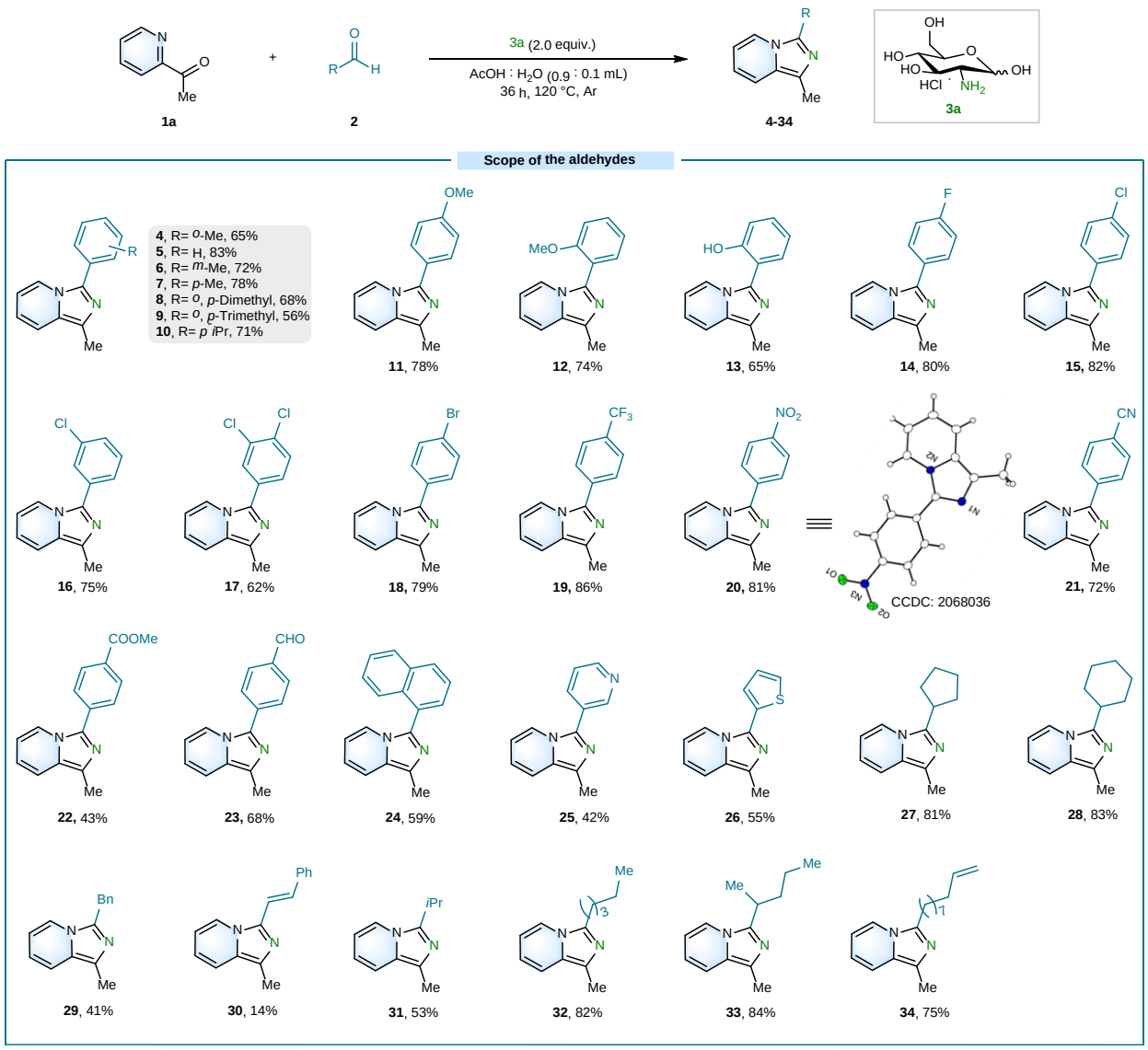


Figure 24 Scope of aldehydes. Reactions were carried out at 120 ˚C with 2-acetylpyridine, aldehydes, D-glucosamine·HCl (**3a**) in AcOH : H_2O (0.9 mL : 0.1 mL), under Ar gas with stirring for 36 h. Yields are those of the isolated product.

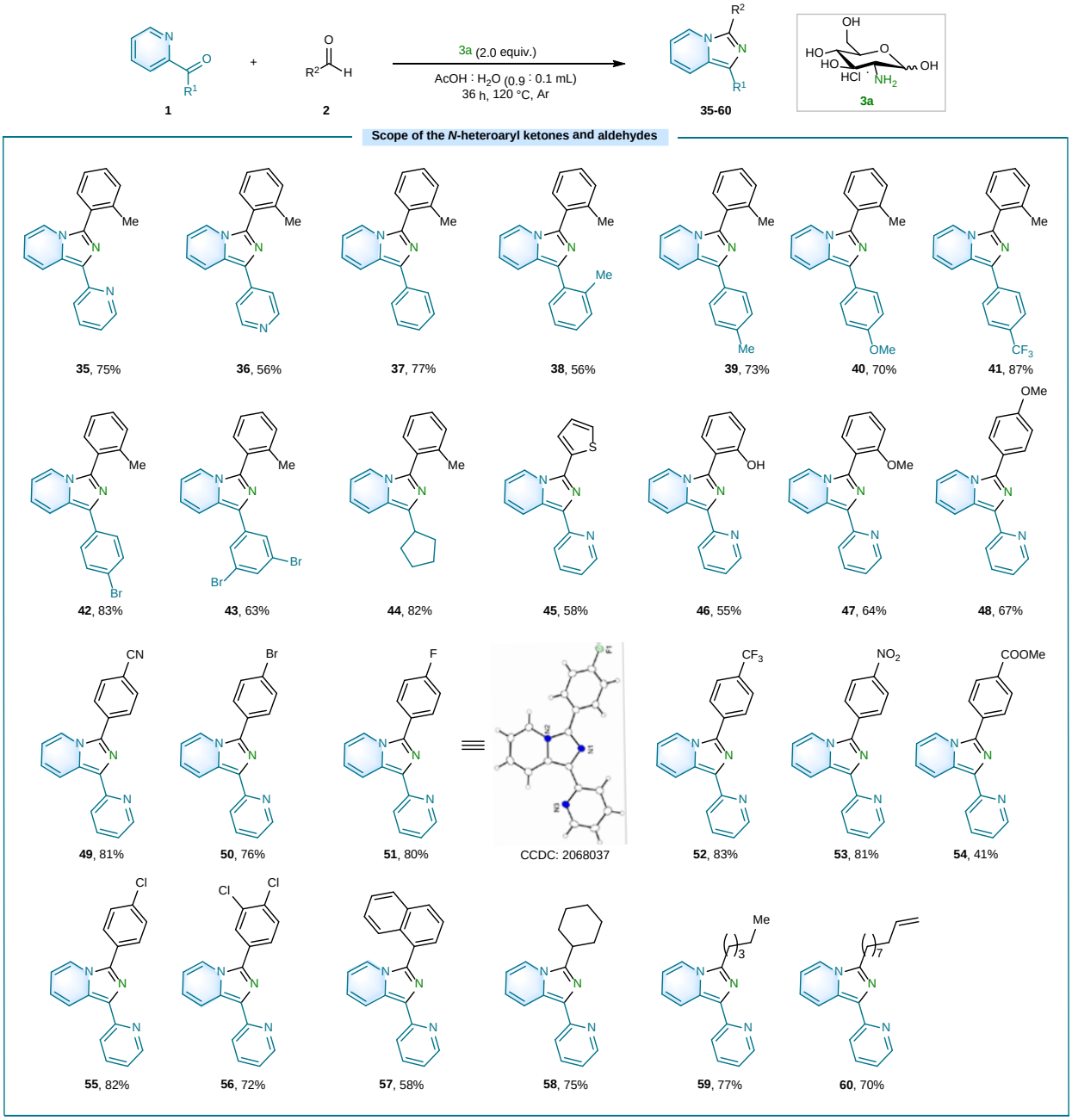


Figure 25 Scope of *N*-heteroaryl ketones and aldehydes. Reactions were carried out at 120 ˚C with *N*-heteroaryl ketones, aldehydes, D-glucosamine·HCl (**3a**) in AcOH : H_2O (0.9 mL : 0.1 mL), under Ar gas with stirring for 36 h. Yields are those of the isolated product.

3.1.4 Applications

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 bi-functionalization of dialdehyde (product **61**) was achieved smoothly (**Figure 26a**). Motivated by this result, 1,4-phenylenebis(pyridin-2-ylmethanone) (product **62**) was also prepared *via* our synthetic route (**Figure 26b**). 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 (**Figure 26c**-**26d**). Moreover, imidazo[1,2-a:3,4-a']dipyridin-10-ium (**65**) was accessed concisely after two steps with standard conditions (**Figure 26e**).

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.[251-254] The first deuterated drug, deutetrabenazine, was approved by FDA in 2017.[255] 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 building blocks of imidazo[1,5-a]pyridines derivatives are highly desired.

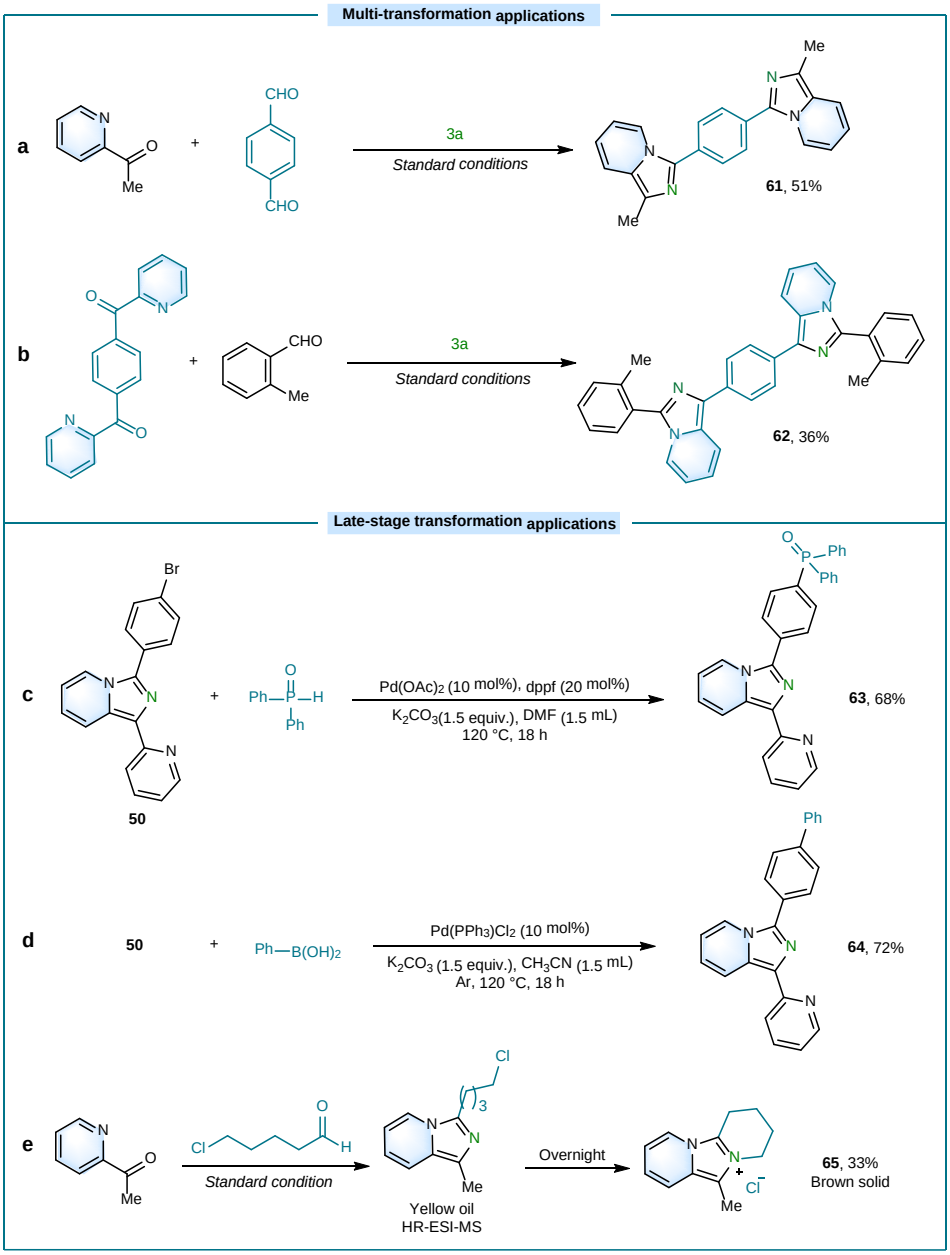


Figure 26 Synthetic applications. **(a)**, **(b)** Multi-transformations of aldehyde and *N*-heteroaryl ketone. **(c)**-**(e)** Late-stage transformation of imidazo[1,5-a]pyridine.

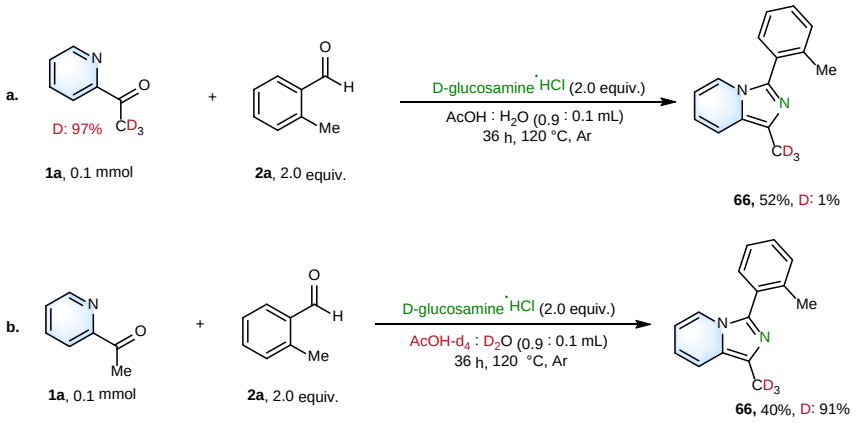


Figure 27 H/D exchange experiments.

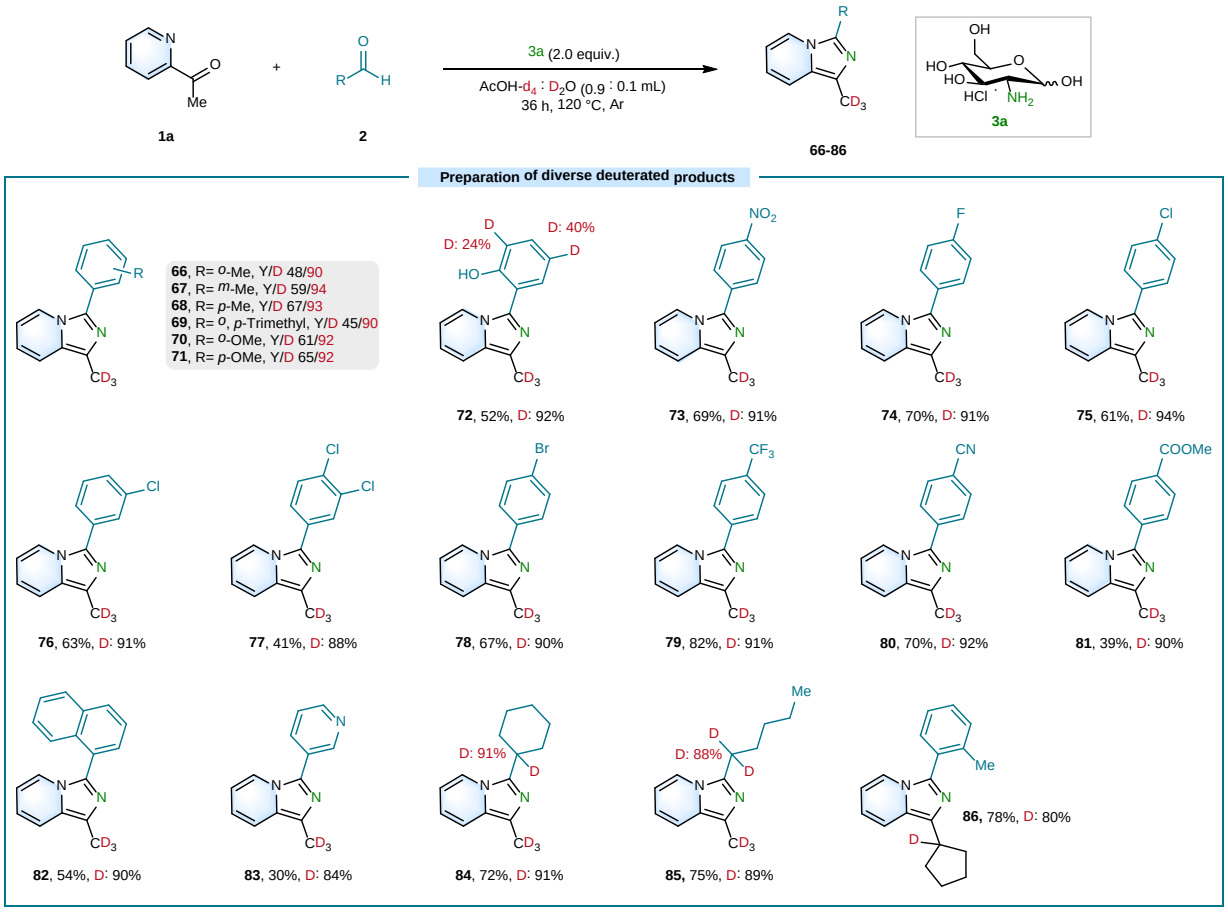


Figure 28 One-pot synthetic applications for diverse deuterated imidazo[1,5-a]pyridines. All yields are isolated products and the D incorporation was measured by ^{1}H-NMR analysis.

The protons at the α-position of pyridine ketone and aliphatic aldehydes could reversibly exchange with acidic aqueous surroundings (**Figure 27**). With our protocol, deuterated imidazo[1,5-a]pyridines were readily synthesized *via* a 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 (**66**-**81**) (**Figure 28**). 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.[256] The calculations of the PMI for our current work as well as for representative approaches are shown comparatively[234],[237-239] (**Figure 29**). The PMI_{RRC} (expressed as 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[237] is higher than ours and the other two approaches.[234],[238,239] 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.

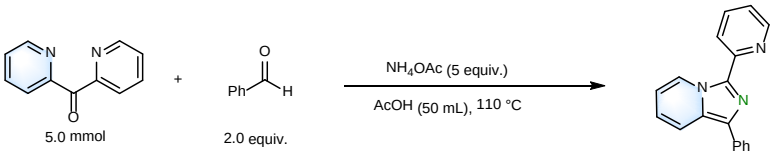
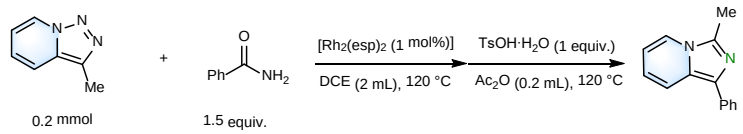
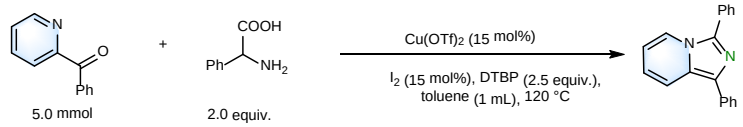
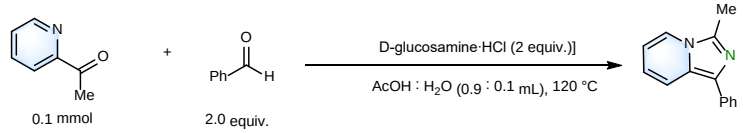
Ref.	Representative approaches	Yield	PMI_{RRC} g·g^{-1}	PMI_{Solv} g·g^{-1}	PMI g·g^{-1}
236		81%	3.6	47.8	51.4
239		73%	3.4	87.0	90.4
240		93%	3.8	0.7	4.5
This work		83%	4.4	60.5	64.9

Figure 29. The calculations of process mass intensity.

3.1.5 Mechanistic studies

To gain insight into the mechanism, a set of control experiments were conducted **(Figure 30-31**). D-glucosamine is able to form imines and azomethines with aldehydes and ketones[85] and the hydroxyl groups of D-glucosamine can be modified *via* substitution reactions.[51] In the first group of control experiment, intermediates **3j** and **3k** were used to verify the reaction order (**Figure 30a-30b**).[85,257] As a result, product **13** was detected *via* ^{1}H-NMR spectroscopy and further confirmed *via* HR-ESI-MS (**Figure 30a**), while product **4** was not detectable (**Figure 30b**). We therefore suggest that D-glucosamine reacted with aldehyde at first to form the imine intermediate.

In the second group of control experiment, *N*-acetyl-D-glucosamine was examined under standard conditions (**Figure 30c**). The results rule out the cleavage pathway *via N*-acetylation of D-glucosamine. In the absence of aldehyde and 2-acetylpyridine, only traces of ammonium acetate were detected by ^{1}H-NMR (**Figure 30d**). The ammonium acetate was further verified by two-dimensional ^{1}H-^{15}N-heteronuclear single quantum coherence (HSQC)-NMR measurement (**Figure 31**), 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 (**Figure 30e**). The isolation of furanoses is rather difficult due to the unstable properties under the acidic conditions at high temperature (**Figure S25** of **Publication 1**). A group of molecules can be detected (99 g/mol, 131 g/mol and 159 g/mol *et al.*). 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 D-glucosamine in this approach, furanose with a pending aldehyde group and hydroxyl groups represents an interesting starting material for platform chemicals including synthesis of furanose sugars,[258] nucleophilic substitution at the anomeric position of furanose,[259] equilibrium and non-equilibrium furanose selection in the ribose isomerization network[260] and synthesis of furanose-based carbohydrates.[261]

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 (**Figure 30f**).[262] 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 (**Figure 30g**).

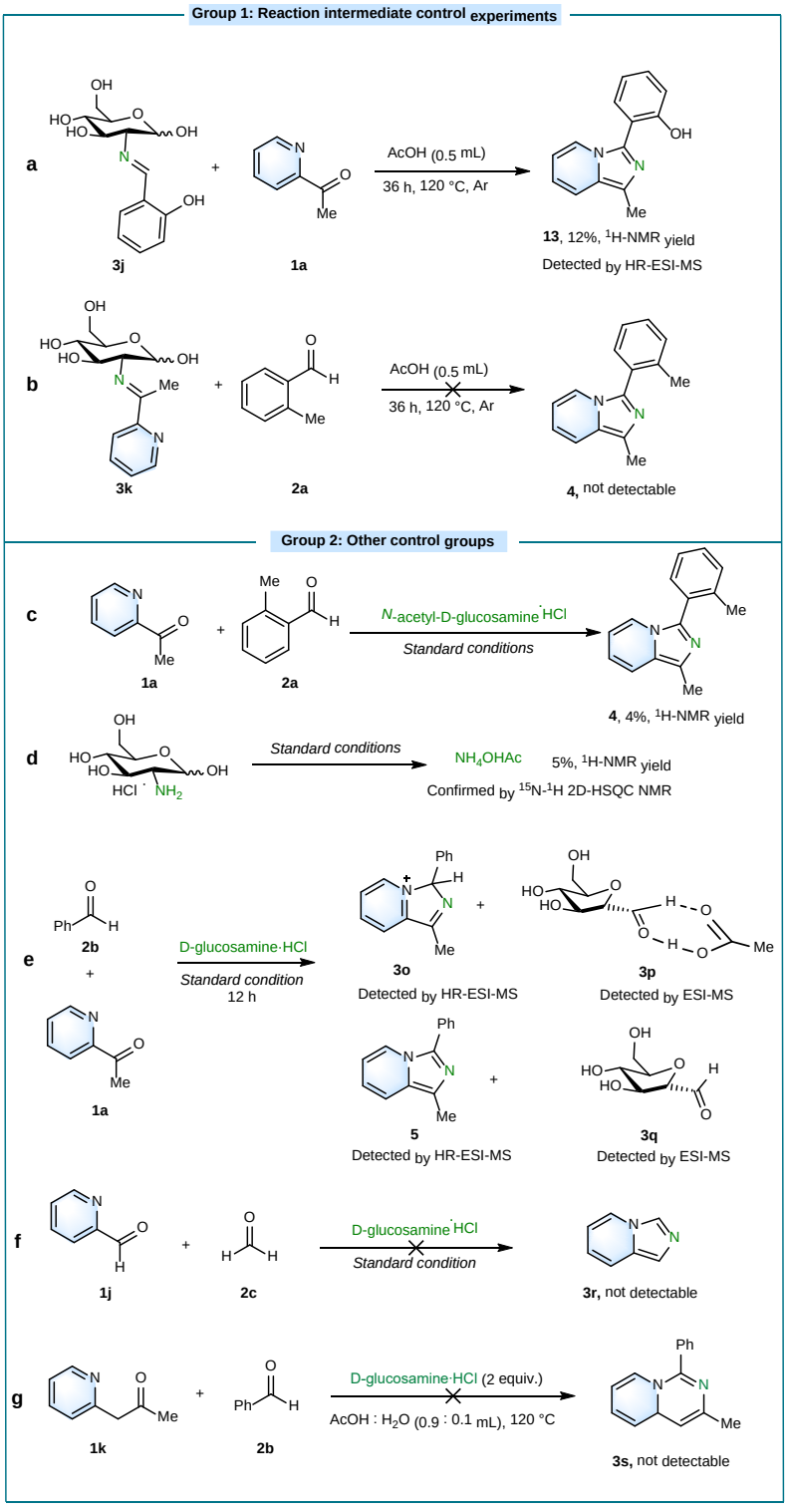


Figure 30 Reaction pathway control experiments.

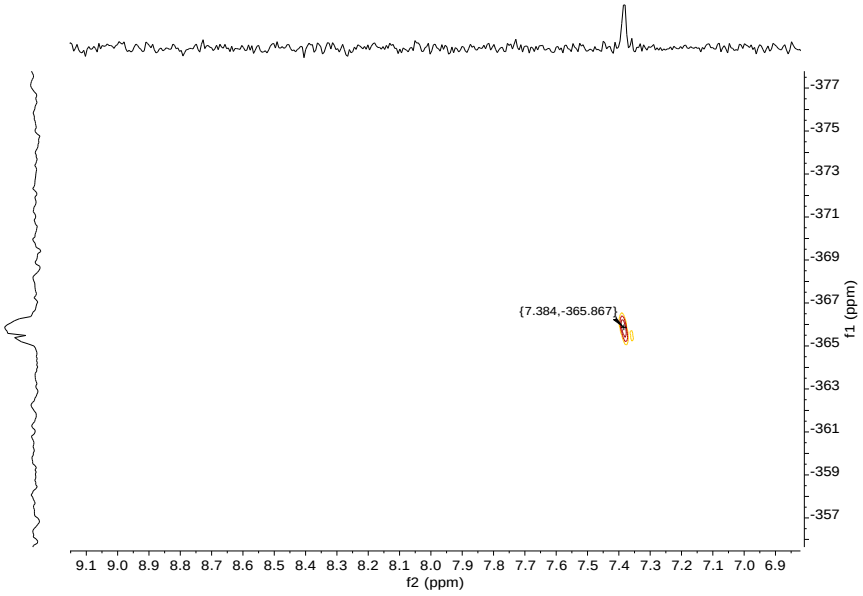


Figure 31 2D-$^{15}N^{1}H$-HSQC-NMR analysis of ammonium acetate in CH_3OH-d_4.

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 **Figure 32a-32b**). **3b** and **3c** show stable and pure β-anomer and α-anomer structures, respectively, while the anomer of D-glucoseamine 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 **Figure 30**, plausible reaction pathways for TS_α and TS_β are proposed in **Figure 32** 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 (**Figure 32a**). 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 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 *via* hydrogen bond between the acetyl group of the β-anomer and the acetate anion (**Figure 32b**). The *E* isomer of imine forms more easily,[85] 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_β) shows a disfavorable alignment with the aromatic ring. The energy states of both TS_α and TS_β *via* D-glucosamine were calculated by electronic structure calculations (**Figure 33b**). Hence, based on the results shown in **Figure 23**, **30** and **32**, a seven-membered ring of α-anomer transition state

(TS_α) formed *via* hydrogen bonds, which favors the following cleavage of C−N bond.[263-265] Combining all results, a plausible mechanism is proposed (**Figure 33a**). 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**.[266] 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 favorable alignment with the seven-membered ring. Due to the unstable transition state of **F**, **H** forms rapidly *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 **Figure 33b**) was 0.9 kcal/mol, which is lower than that of the β-anomer (**TS_β**). Since the Gibbs free energies of reactant connected to **TS_α** (**D_α**) was 0.7 kcal/mol higher than that connected to **TS_β** (**D_β**), 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 taken as the actual barrier difference. The acetate molecule stabilizes the transition state via the hydrogen bond as depicted in **Figure 32a**, which is ultimately transferred. The ring system, as schematically shown in **Figure 32b**, aligns with the carboxylic group *via* dispersion forces that could reduce the barrier. This stands as a further example for the importance of London forces in stereoselectivity.[267]

The α/β-ratio for the mixture of D-glucosamine and HCl was determined using the same theoretical method. Three conformers (**Figure 33c**) 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 **Figure 33c**. 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.

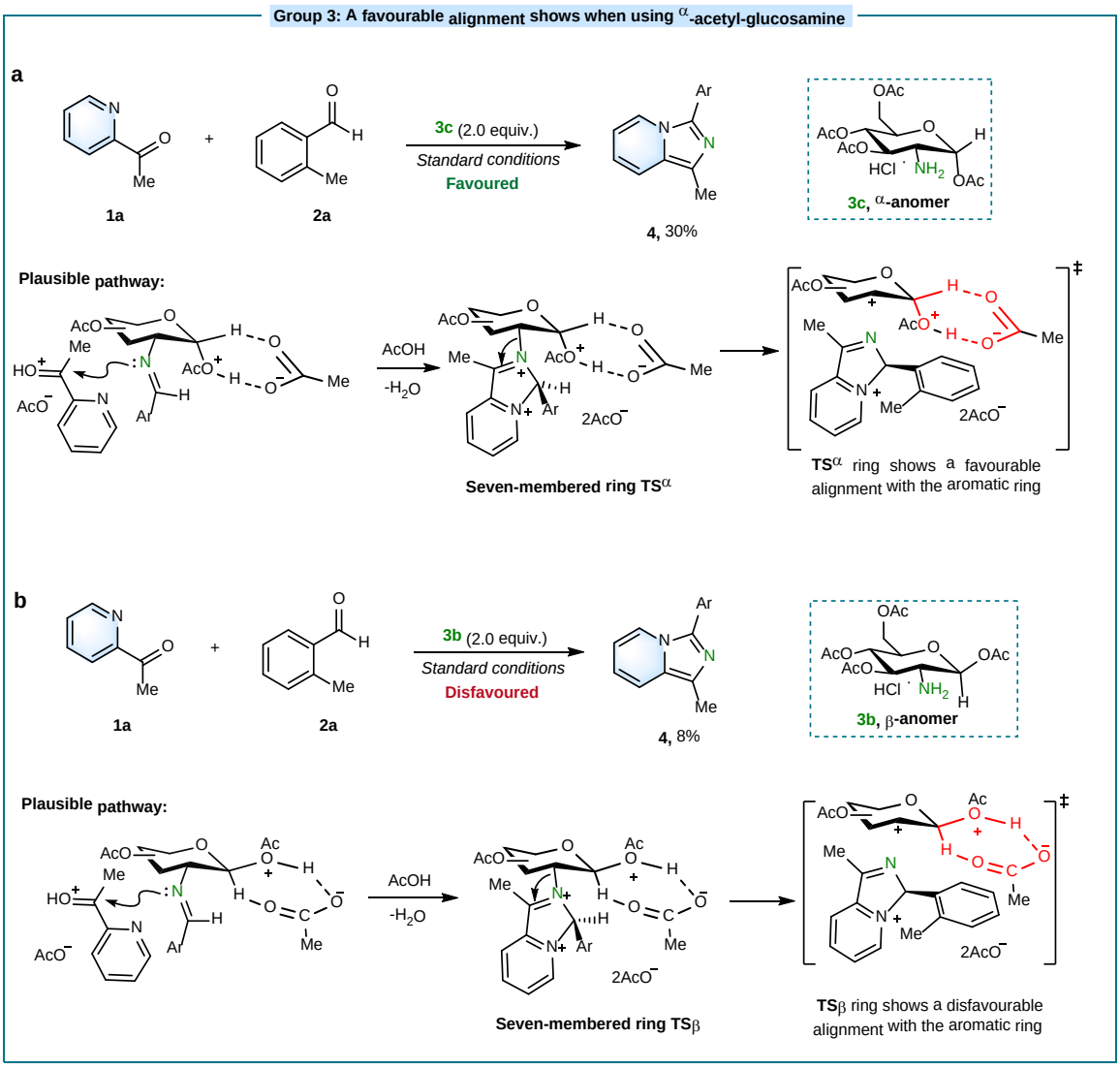
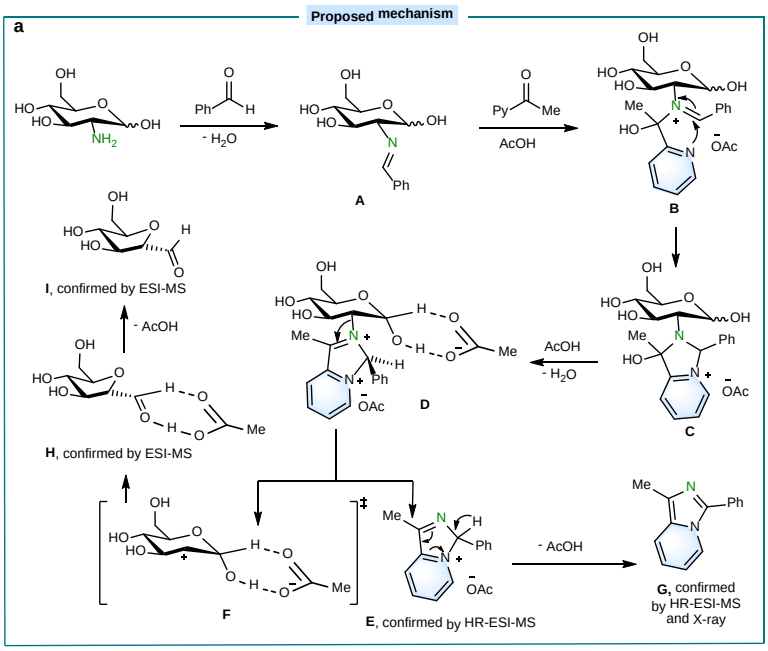
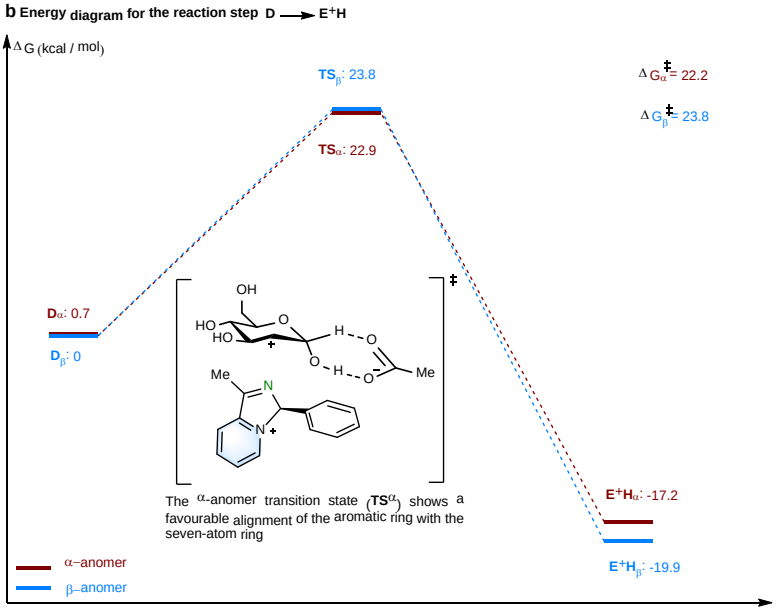
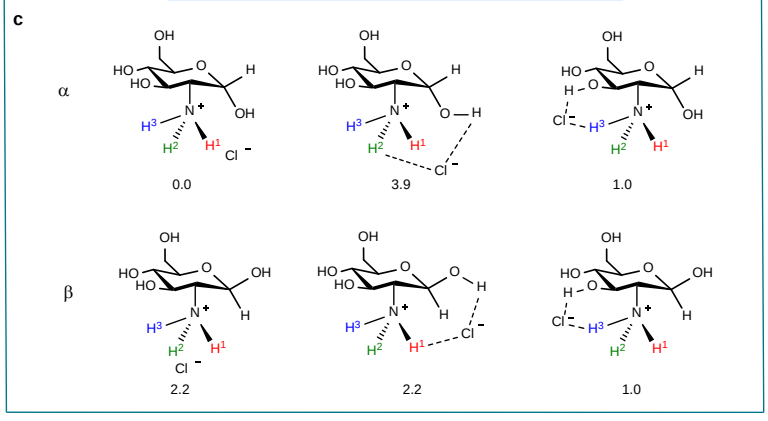


Figure 32 Anomeric stereoauxiliary control experiments.


Proposed mechanism
a
- H2O
AcOH
A
B
C
D
E, confirmed by HR-ESI-MS
F
G, confirmed by HR-ESI-MS and X-ray
H, confirmed by ESI-MS
I, confirmed by ESI-MS
- AcOH
AcOH
- H2O


b Energy diagram for the reaction step D ⟶ E+H
ΔG (kcal / mol)
TSβ: 23.8
TSα: 22.9
ΔGα‡ = 22.2
ΔGβ‡ = 23.8
Dα: 0.7
Dβ: 0
The α-anomer transition state (TSα) shows a favourable alignment of the aromatic ring with the seven-atom ring
E+Hα: -17.2
E+Hβ: -19.9
α–anomer
β–anomer


c
Computed DFT conformers for the mixture of D-glucosamine and HCl
α
β
0.0
3.9
1.0
2.2
2.2
1.0

Figgure 33 (a) Proposed mechanism. **(b)** Density functional theory calculations. **(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. Conformers in c are v1, v2 and v3 from left to right.

3.2 Publication 2: Direct Nitrogen Interception from Chitin/chitosan for the Preparation of Nitrogen-containing Chemicals

3.2.1 Background

Chitin and chitosan are abundant native linear polymers composed of randomly distributed units, namely, *N*-acetyl-D-glucosamine and D-glucosamine linked by β-1,4-linages.[268] The quantities of *N*-acetyl-D-glucosamine units are generally more than 50% in chitin backbone, while chitosan contains less than 50% *N*-acetyl-D-glucosamine.[52,269,270] Human processing of sustainable chitin-containing raw materials, such as crustaceans shells, exhibits only a very minor fraction of all the chitin produced annually in nature,[271-276] while the major fraction maintains intact.[36] On the other hand, low molecular weight nitrogen-containing chemicals (NCCs) play a pivotal role in modern life, from pharmaceutical, agriculture and food fields to material fields.[12,277-280] The nitrogen source of prevailing industrial processes for NCCs is mainly from NH_3, NO_3^- and NO_2^- etc., which are obtained from N_2 fixation.[281-289] The quantities of nitrogen element fixed annually in chitin *via* the biochemical process are much more than the N_2 fixed in the Haber-Bosch process.[13] Therefore, the transformation of renewable chitin containing fixed nitrogen into value-added NCCs has drawn much attention.[12]

Four types of strategies are currently known for the activation of amines in chitin/chitosan (**Figure 34a**). The first strategy **(i)** referred to the direct modifications of amines on the chitosan/chitin backbones without C–N bond cleavage.[271] The second strategy **(ii)** involves the cleavage of C–N bonds *via* strong oxidants or acidic conditions with the simultaneous release of N_2 or limited types of organic and primarily inorganic low-value NCCs, such as acetamide and ammonium salts.[116,290,291] These two strategies cannot generate value-added NCCs, in particular more complicated organic compounds, which are highly desired in the modern life. Recently, the third strategy **(iii)** emerges with the biorefinery by converting chitin/chitosan into a preliminary C6 backbone *via* a depolymerization (e.g. monomeric and oligomeric molecules) and by further conversion of the C6 backbone into diversified products *via* breakage and

rearrangement (e.g. 3-acetamido-5-acetylfuran et al.).[12,13] Although various protocols have been established through enzymatic, catalytic and/or hydrothermal treatments pathway, only more than 10 NCCs examples (including sugars derivatives, amino alcohols, furanic amides) have been obtained with complicated conditions and a low efficiency. The fourth strategy **(iv)** involves the cleavage of C–N bond

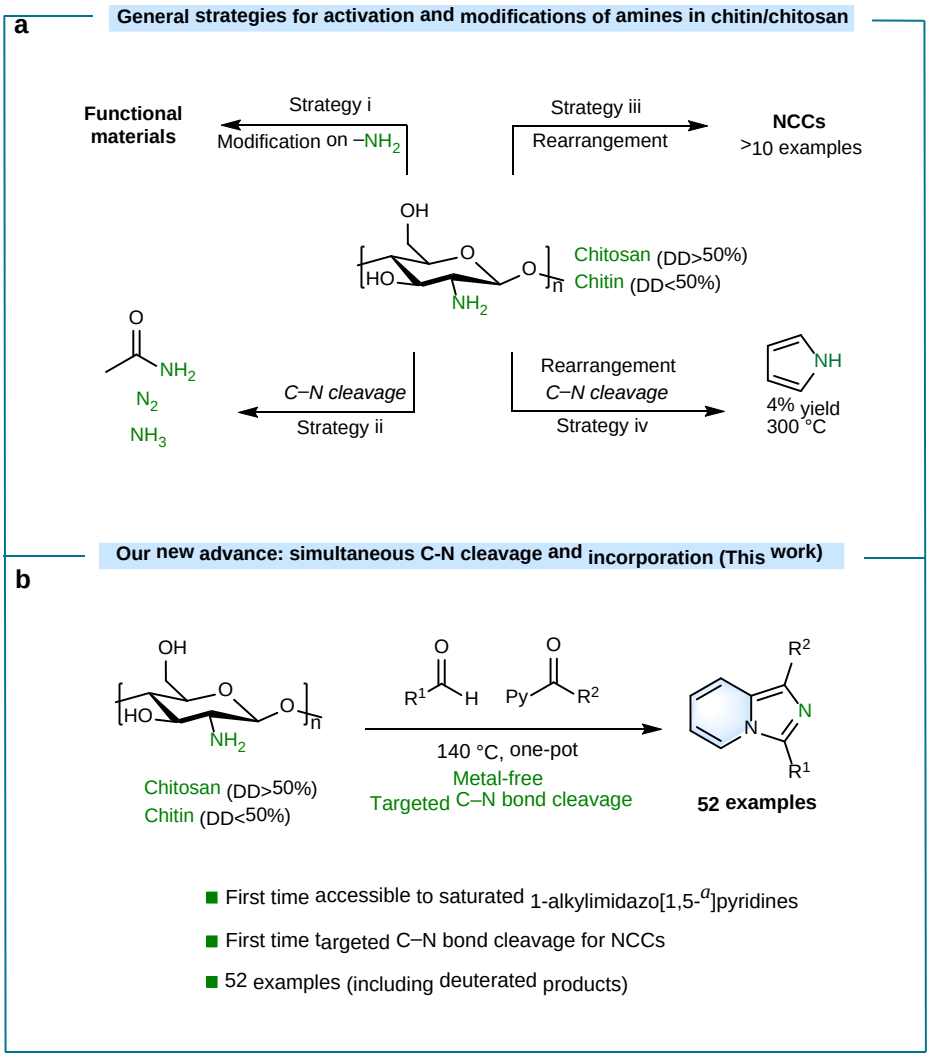


Figure 34 a) General strategies for activation of amines in chitin/chitosan. **b)** This work: direct incorporation of nitrogen from chitosan/chitin for imidazo[1,5-a]pyridines.

of chitin for the assembly of pyrrole with a low yield of 4%, which was realized in alkali aqueous solution at 300 ºC in 2016.[115] 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

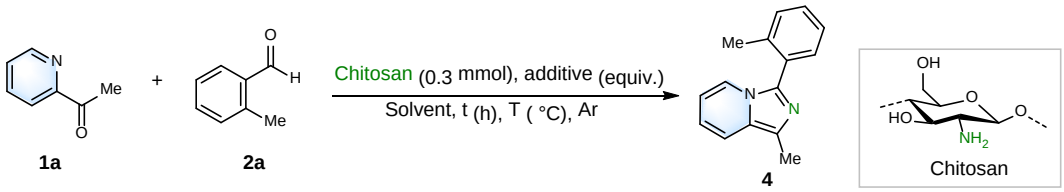
for the construction of *N*-heterocycles from biomass.[292-294] The C–N bond of chitin/chitosan that offers a potential reactive site for various versatile chemical diversifications generally remains intact. Therefore, a one-pot protocol enabling the targeted efficient incorporation of nitrogen from chitin/chitosan into diverse valuable NCCs like *N*-heterocycles is highly attractive, which will advance the existing methodologies while expanding the library of NCCs derived from renewable sources.

Herein, we developed an efficient catalyst-free one-pot protocol for the direct integration of nitrogen from the renewable feedstock chitosan/chitin that yields various valuable imidazo[1,5-*a*]pyridines (52 examples with yields up to 92%) under mild conditions (**Figure 34b**), which provides ready access to 1-alkylimidazo[1,5-*a*]pyridines (39 examples) and 1-arylimidazo[1,5-*a*]pyridines (13 examples).

3.2.2 Optimization studies

We initiated our studies by using 2-acetylpyridine (**1a**) and 2-methylbenzaldehyde (**2a**) as substrates to evaluate the envisioned nitrogen interception from chitosan for desired imidazo[1,5-*a*]pyridine **3** employing metal-free condition. At the outset, product **4** was observed by ^{1}H NMR analysis on a condition with solvent mixture of AcOH/H_2O (0.9/0.1 mL) (**Table 4**, entries 1-2). After that, several silver salt additives were investigated. Interestingly, the yield of **4** was increased obviously from 3% to 13% when the silver trifluoroacetate (AgTFA) was exploited, while silver acetate (AgOAc) was not helpful for the efficacy (**Table 4**, entries 3-4). These results indicated that the anion ion $^-OCOCF_3$ in AgTFA might facilitate the transformation. Therefore, a solvent mixture of CF_3COOH/H_2O (0.9/0.1 mL) was employed as a substitute of the previous solvent AcOH/H_2O (0.9/0.1 mL). To our delight, the yield was improved to 29% when CF_3COOH/H_2O was used as reaction media (**Table 4**, entry 5). Then, a higher yield (61%) was achieved with CF_3COOH (1.0 mL) as the solvent (**Table 4**, entry 6). Besides, diverse reaction temperatures, ranging from 90 ºC to 140 ºC, were examined (**Table 4**, entries 7-8). Thus, the optimal temperature was determined to be 140 ºC and a 78% yield was obtained. Moreover, the reaction was conducted at 12 h, 24 h and 36 h with the yield of 31%, 59% and 78%, respectively. The lower equivalent of chitosan leads to inferior yield. Combining all factors regarding the equivalent of chitosan, reaction temperature and time, the optimal reaction condition was identified as shown in entry 8: 140 ºC for 36 h (**Table 4**).

Table 4. Optimization of the reaction conditions



Entry	Additives	Solvent (mL)	t(h) / T(ºC)	Yield (%)[a]
1	-	AcOH	36 / 120	n.d.
2	-	AcOH : H_2O (0.9 : 0.1)	36 / 120	3
3	AgTFA	AcOH : H_2O (0.9 : 0.1)	36 / 120	13
4	AgOAc	AcOH : H_2O (0.9 : 0.1)	36 / 120	<1
5	-	CF_3COOH : H_2O (0.9 : 0.1)	36 / 120	29
6[b]	-	CF_3COOH (1.0)	36 / 120	61
7[b]	-	CF_3COOH (1.0)	36 / 90	4
8[b]	-	**CF_3COOH (1.0)**	**36 / 140**	**78**
9[b]	-	CF_3COOH (1.0)	12 / 140	31
10[b]	-	CF_3COOH (1.0)	24 / 140	59
11[b, c]	-	CF_3COOH (1.0)	36 / 140	66

[a] Reactions were carried out with chitosan (0.2 mmol based on AGU 161 g/mol), 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (0.2 mmol) and solvent (1.0 mL). Yields were determined by ^{1}H-NMR analysis with CH_2Br_2 as the internal standard. [b] Chitosan was dried at 100 °C oven overnight. [c] Chitosan (0.2 mmol per AGU).

3.2.3 Scope of substrates

With the optimized reaction conditions in hand, we next explored the versatility of metal-free nitrogen interception from chitosan with various aldehydes for NCCs (**Figure 35**). Firstly, a series of aromatic aldehydes, including those having electron-donating or electro-withdrawing groups at different positions (*ortho*, *meta* or *para*) were subjected to the optimized conditions. As a result, these aldehydes could be efficiently transformed into the corresponding products **4**-**23** and **61**. Aldehydes with electro-donating groups, such as methyl, isopropyl and methoxy group (**4**-**12**), are well compatible with the transformations, while a lower yield was obtained for substrate with hydroxyl group (**13**). In addition,

electro-withdrawing substituents, including halogen and trifluoromethyl groups, were well accommodated. Moderate yields were achieved for aldehydes with nitro and nitrile groups. It is noteworthy that the challenging *para*-dialdehyde also delivered the corresponding products with diverse conditions (**23** and **61**). Furthermore, (*E*)-3-(4-(dimethylamino)phenyl)acrylaldehyde (**87**), 1-naphthaldehyde (**24**), nicotinaldehyde (**25**) and thiophene-2-carbaldehyde (**26**) were also amenable in our protocol. In addition to aromatic aldehydes, those aliphatic aldehydes (**28, 30, 31** and **33**) were well compatible with the conditions.

We further investigated the viable scope of differently substituted pyridine ketone **1** as the general coupling partners for this transformation (**Figure 36**). The di(pyridin-2-yl)methanone and phenyl(pyridin-2-yl)methanone were well compatible with the protocol (**35** and **37**). Pyridine ketones with electron-donating groups (**38**-**40**) or electron-withdrawing groups (**41**-**43**) displayed good reactivity and delivered the corresponding products efficiently. These results indicated that the current protocol was not sensitive to the electronic or stereoscopic properties of pyridine ketones. Moreover, aliphatic cyclopentyl(pyridin-2-yl)methanone (**44**) was also transformed efficiently.

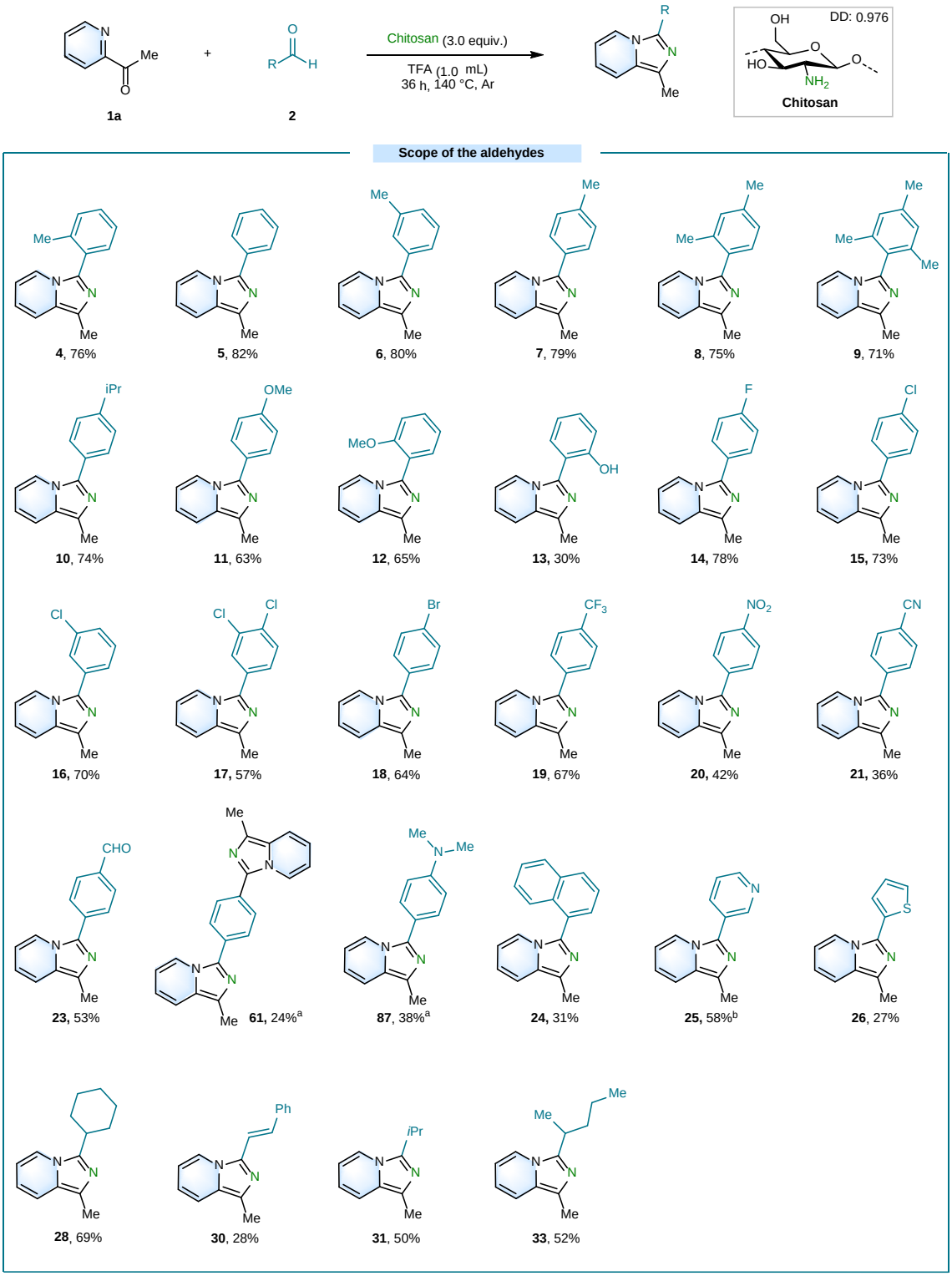


Figure 35 Scope of aldehydes for synthesis of imidazo[1,5-a]pyridines. A mixture of 2-acetylpyridine (0.1 mmol), aldehydes (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Yields are those of the isolated

products. [a]2-acetylpyridine (0.1 mmol), aldehyde (2.0 equiv.), chitosan (3.0 equiv) and CF_3COOH (0.7 mL), 4 days. [b]2-acetylpyridine (0.1 mmol), aldehyde (4.0 equiv.), chitosan (2.5 equiv) and CF_3COOH (0.7 mL), 36 h.

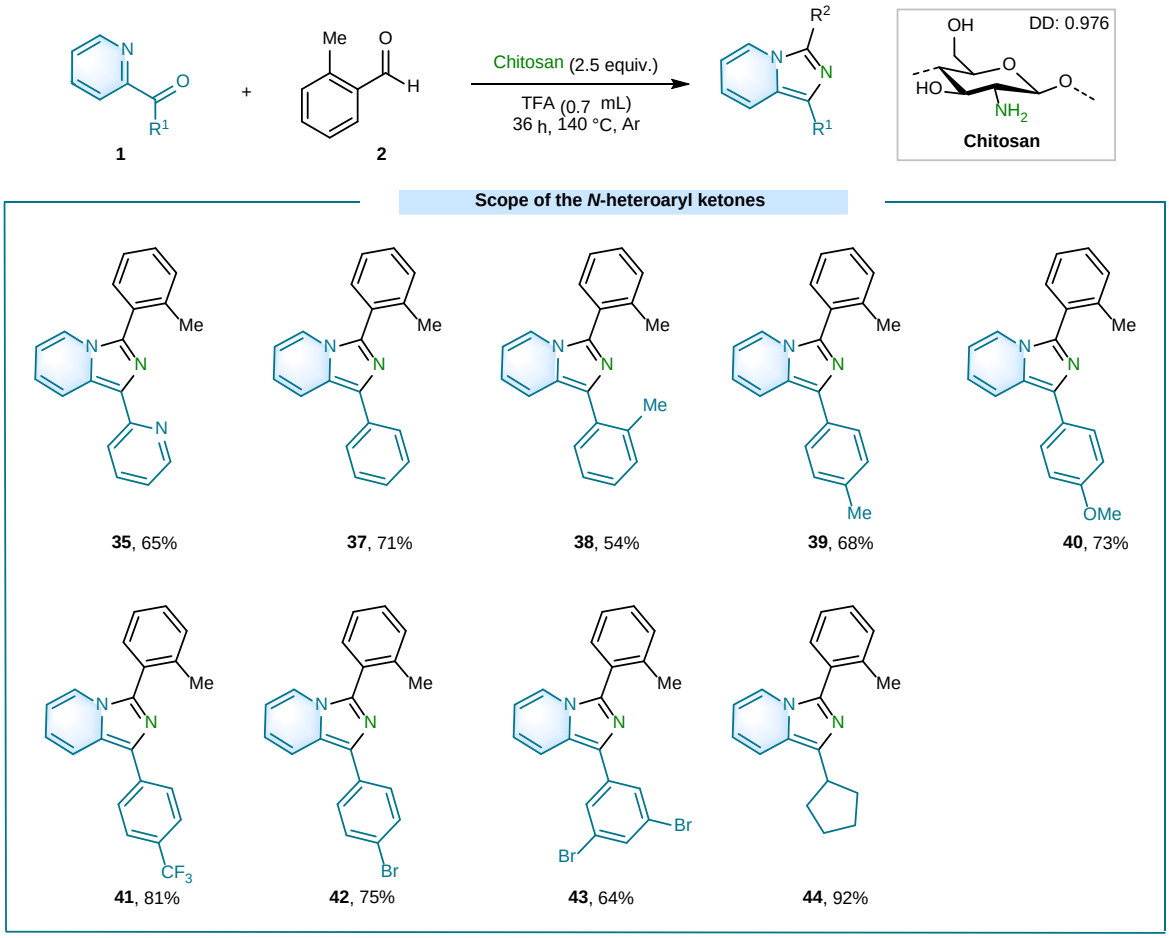


Figure 36 Scope of the pyridine ketones for synthesis of imidazo[1,5-a]pyridines. A mixture of pyridine ketone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Yields are those of the isolated products.

3.2.4 Applications

N-heterocyclic compounds play an important role in materials and organic synthesis fields, especially as ligands in chemical transformations. Thus, the utilization of a sustainable protocol for the assembling of *N*-heterocyclic tridentate ligands is highly desirable. Herein, these tridentate ligands, 2-(1-(pyridin-2-

yl)imidazo[1,5-a]pyridin-3-yl)phenol (**46**) and 3-(2-methoxyphenyl)-1-(pyridin-2-yl)imidazo [1,5-a]pyridine (**47**), were accessed concisely through the interception of nitrogen from chitosan which further demonstrates the practical synthetic use of our method (**Figure 37**).

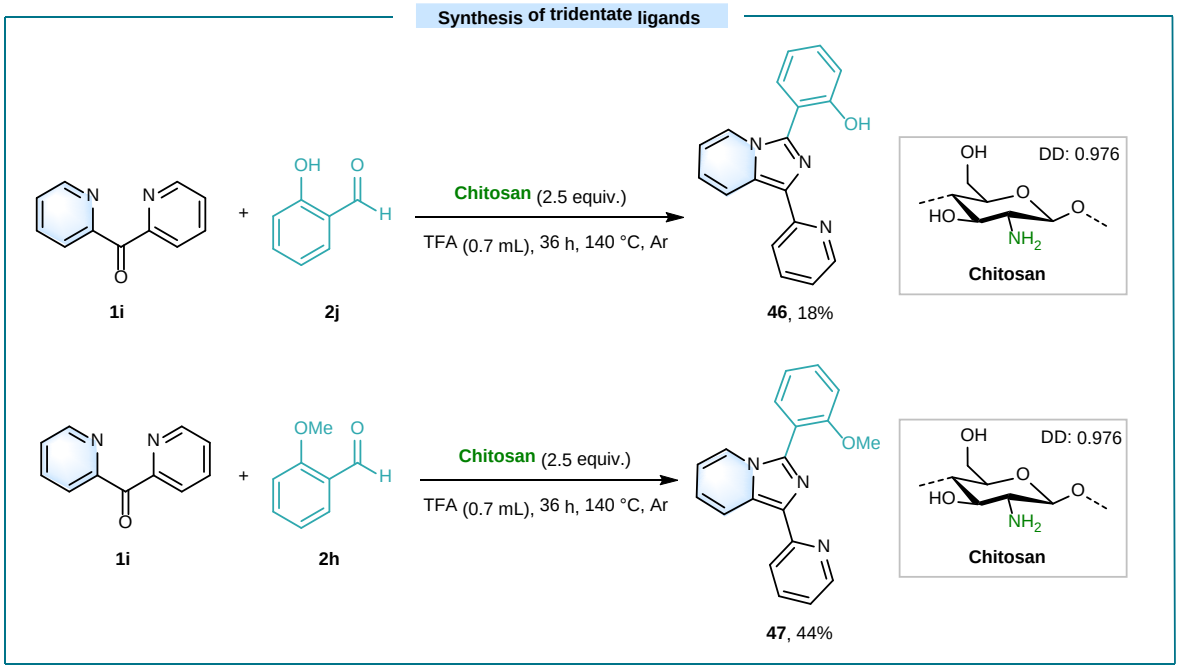


Figure 37 Synthesis of value-added tridentate ligands *via* incorporation of nitrogen from renewable chitosan. A mixture of di(pyridin-2-yl)methanone (0.1 mmol), aldehydes (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Yields are those of the isolated products.

Isotope labeling showed important applications on drug absorption, distribution, metabolism and excretion.[251,252,255] Inspired by the H–D exchange between α-C–H of pyridine ketone and CF_3COOD solvent, a variety of C(sp^3)–H deuterated imidazo[1,5-a]pyridines derivatives was synthesized in one-pot procedure (**Figure 38**). Those aromatic aldehydes, pyridine aldehyde and cyclic aliphatic aldehyde were synthesized with deuterated incorporation of products (**45-54**). In addition, it is worth noting that the proton of the aromatic aldehyde with a hydroxy group and methoxy group could also be deuterated under this condition (**46-48**).

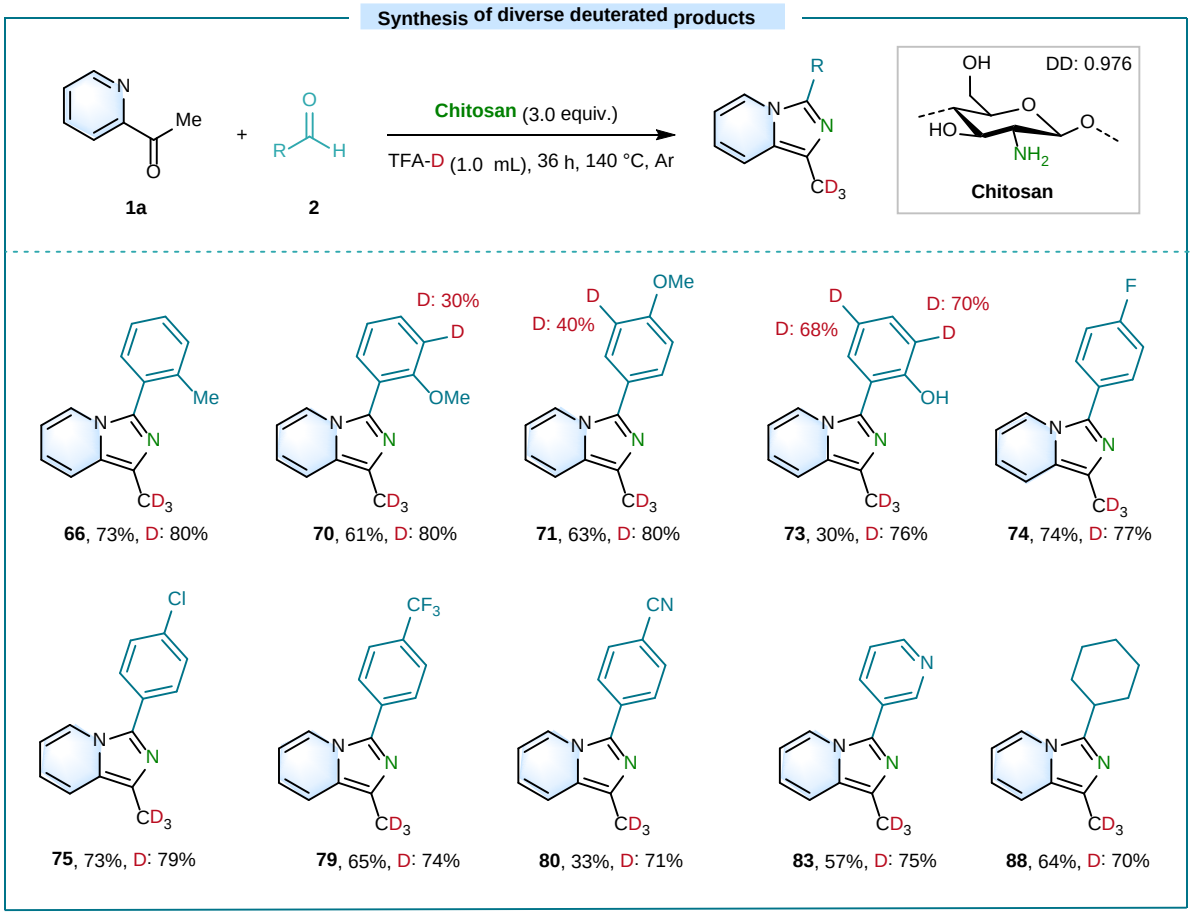


Figure 38 One-pot synthesis of deuterated C(sp^3)–H bonds of imidazo[1,5-a]pyridine derivatives *via* incorporation of nitrogen from renewable chitosan. A mixture of 2-acetylpyridine (0.1 mmol), aldehydes (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Yields are those of the isolated products. D incorporation was tested by ^{1}H-NMR analysis.

3.2.5 Synthesis of NCCs with chitin

Furthermore, sustainable biomass chitin is proved to be a viable nitrogen source as well in this transformation, which could further bypass the deacylation process from chitin to chitosan and make the reaction more useful (**Figure 39**). As a result, a group of imidazo[1,5-a]pyridines were obtained under the standard conditions, including **3** (71%), **13** (71%), **15** (53%), **23** (29%), **26** (17%), **31** (26%), **39** (89%) and **41** (16%). Using chitosan as nitrogen sources in Fig. 2-5, these products can be obtained with higher yields, including **3** (76%), **13** (78%), **15** (70%), **23** (31%), **26** (28%), **31** (65%), **39** (92%) and **41** (44%). Despite the more advantages for these NCCs by chitin than chitosan, compared the yields of these

products by chitin with these by chitosan, chitosan shows better reaction efficiency to obtain higher yield of these products.

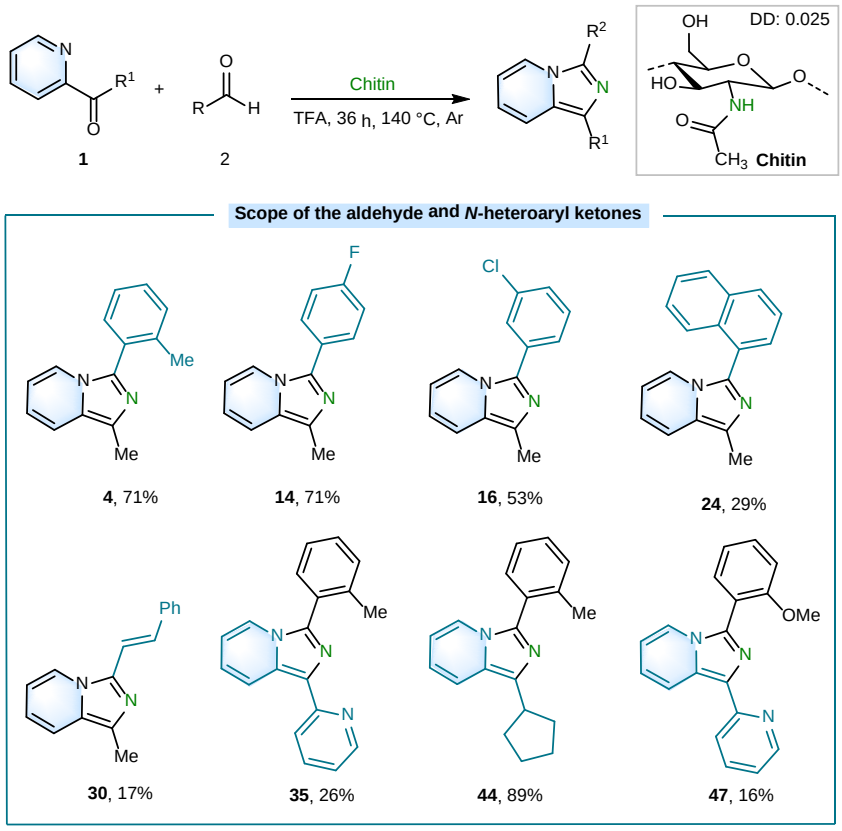


Figure 39 Direct utilization of chitin for the synthesis of imidazo[1,5-a]pyridines. Method for products **3**, **13**, **15**, **23** and **26**, a mixture of 2-acetylpyridine (0.1 mmol), aldehydes (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Method for products **31**, **39** and **41**, a mixture of pyridine ketones (0.1 mmol), aldehydes (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Yields are those of the isolated products.

3.2.6 Mechanistic studies

11% of ammonium was trapped *via* ^{1}H-NMR analysis, which could provide a support for the mainly release of nitrogen after the condensation to an intermediate, such as imidazo[1,5-*a*]pyridine-2,4-diium or imidazo[1,5-*a*]pyridin-4-ium (**Figure 40a**). Besides, an imidazo[1,5-*a*]pyridin-4-ium **4'** was confirmed by ESI-HRMS analysis (calc. for $C_{15}H_{15}N_2^+$ [M]: 223.1230, Found: 223.1232) (**Figure 40b**), which reveals a

pathway for imidazo[1,5-*a*]pyridine **4** *via* deprotonation of **4'**. Based on the control experiment (Figure **40a**-**40b**), a plausible reaction pathway was proposed. First, deacetylation takes place which enables the transformation of chitin to chitosan.[295] Then, an imine intermediate is generated *via* the dehydration between an aldehyde substrate and an amine group of chitosan. The imine intermediate attacks a pyridine ketone substrate to form an iminium intermediate. Next, an imidazo[1,5-*a*]pyridine-2,4-diium intermediate forms *via* the intramolecular nucleophilic addition between pyridine and iminum in the backbone of iminium intermediate.[296] With the help of TFA, the imidazo[1,5-*a*]pyridine-2,4-diium transfers to an imidazo[1,5-*a*]pyridin-4-ium (**Figure 40b**) *via* plausible pathways of dehydration and C–N bonds cleavage. Finally, an imidazo[1,5-*a*]pyridine generated *via* the deprotonation of the imidazo[1,5-*a*]pyridin-4-ium.

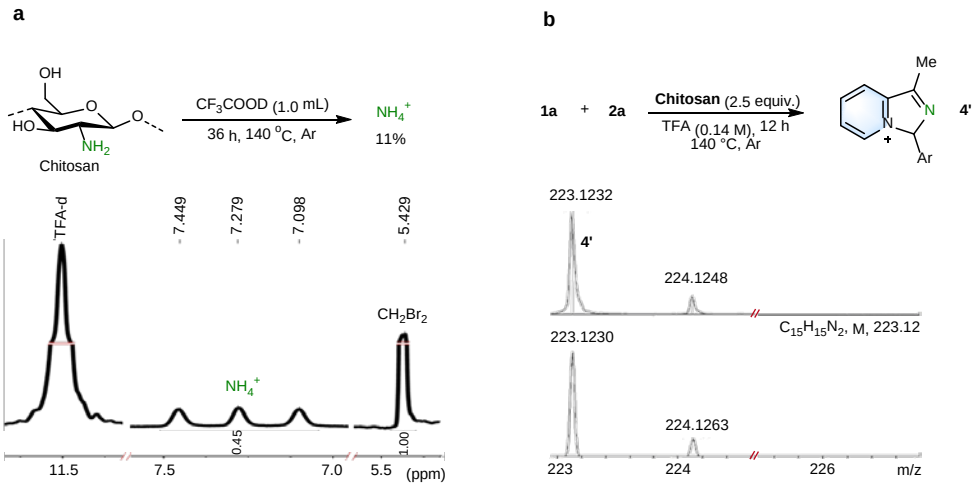


Figure 40 Control experiments. **(a)** Control experiment for thermal deamination. **(b)** ESI-HRMS analysis of intermediate.

3.3 Publication 3: Anomeric Stereoauxiliary-organocatalyzed One-pot Site-selective C_2-aldehylation for Trisubstituted Indolizine-2-carbaldehydes

3.3.1 Background

Indolizines are an important group of *N*-heterocyclic compounds that play pivotal roles in pharmaceutics (**Figure 41a**),[297-303] materials science,[304] and chemical feedstocks.[305,306] The easily modifiable carbaldehyde group makes indolizine-carbaldehyde a precursor for versatile indolizine products. Although tremendous progress has been made in the preparation of indolizines mainly by Scholtz

reaction,[307,308] Tschitschibabin reaction,[309,310] pyridinium *N*-methylides,[311,312] and cyclization of alkynes with heteroaromatic compounds,[236,313,314] the chemical construction of indolizine-carbaldehydes with a direct site-selectivity (C_1/C_2/C_3) has been a long-standing challgenge for synthetic chemists.

Various strategies for direct site selectivity on C_1/C_3 of indolizine-carbadlehydes have been reported so far. **i)** Representative strategies for C_1 site-selectivity. In 2018, Li group reported the iron-catalyzed aerobic oxidation of pyridine and allenoate for the preparation of trisubstitued indolizine-1-carbaldehydes.[315] It is highly dependent on specific allenoate substrates with electron-withdrawing groups and the traditional pyridinium *N*-methylides route. **ii)** Representative strategies for C_3 site selectivity. In 1984 and 2017, a four-step synthesis of trisubstituted indolizine-3-carbaldehydes was reported.[316,317] This method first requires the synthesis of indolizines *via* a traditional pyridinium *N*-methylide strategy, followed by the introduction of a carbaldehyde group at the C_3 position *via* a non-green Vilsmeier reagent. In addition, in 2017, Wang group developed a novel amine-*N*-heterocyclic carbene relay catalysis strategy for the preparation of trisubstituted indolizine-3-carbaldehyde.[318] Although indolizine-3-carbaldehyde is efficiently synthesized *via* a relay co-organocatalyst, this method is still limited to pyridine substrates with 2-substituted electron-withdrawing groups, which greatly limites the accessible substrates.

In contrast, there are few effective strategies for the site-selective C_2-aldehylation of indolizine-carbadlehyde, especially for trisubstituted indolizines. In 2016, Biagetti *et al.* synthesized 1,2-disubstituted indolizine-2-carbaldehyde derivatives in 6 steps (**Figure 41b**).[202] Two years later, a monosubstituted indolizine-2-carbaldehyde was prepared in two steps by using a commercial indolizine-2-carboxylic acid, for just one example.[203] However, these two C_2 site-selective strategies are highly rely on multiple synthetic steps using non-green expensive reagents (first four-steps construction of disubstituted indolizines with C_2-substituted carboxyl group *via* precious metal catalyst, followed by introduction of a carbaldehyde on indolizine through reduction and oxidation processes)[202] or expensive and rare commercial feedstocks such as monosubstituted indolizine-2-carboxylic acid (395.57 €/g from Sigma company) *via* amidation and reduction processes.[203] In addition, only a few examples of mono-substituted indolizine-2-carbaldehyde have been constructed, while the high value-added 1,2,3-trisubstituted indolizine-2-carbaldehyde is still not available. In 2021, Zhao *et al.* reported a metal-free catalytic method using acetic acid as a solvent for 2-acylindolizine and indolizine-2-carbaldehydes.[319] This method is limited to internal enones and 1-aryl-indolizine. In particular, the method was significantly less efficient for 1-alkyl-2-acylindolizine (20%-24%) and cyclic indolizine (8%).

Due to the challenges of sensitive functional groups, regioselectivity, and strong steric shielding, there is currently no efficient one-pot method for the construction of 1,2,3-trisubstituted indolizine-2-carbaldehydes derivatives by dehydration [3+2] cyclization of cinnamaldehyde and 2-acetylpyridine. As

the most severe challenge, 2-acetylpyridine readily attacks the carbonyl group of cinnamaldehyde with a base,[240] while 2-acetylpyridine activated by metal-based Lewis acid can attack the β-position of α,β-unsaturated aldehydes in the presence of secondary organoamine as catalysts.[320]

Asymmetric organocatalysis is one of the most thriving research domains in contemporary organic synthesis.[161-166] Until today, aminocatalysis with iminium and enamine catalysis modes has drawn much attention.[178-183,185,186] However, the marjority of chiral skeleton aminocatalysts are provided by artificially designed adjustable steroauxiliary group, which provide strong steric shielding for regioselectivity and stereoselectivity control. Thus, it is attractive to utilize an inexpensive aminocatalyst with a natural charil backbone. Commercially available D-glucosamine as an amino-containing monosaccharide is ubiquitous in nature derived from chitin.[268] Sugar-derived thiourea organocatalysis has only been reported as a few examples.[190-192] Up to now, there are no examples of aminocatalysis using carbohydrates alone. Inspired by the regioselective-controlled aminocatalysis strategy and the different stereochemical structures of α/β-anomers of D-glucosamine, we demonstrate for the first time a novel synthetic strategy using β-anomeric glucosamine as a steroeoauxiliary amincatalyst for one-pot site-selective construction of 1,2,3-trisubstituted indolizine-2-carbaldehydes (**Figure 41c**). To overcome the above challenges, we used Brønsted acids to stabilize the methyl group of 2-acetylpyridine and hinder the deprotonation of the methyl group.[243] In addition, lithium cations are used to stabilize oxygen anions and activate cinnamaldehyde.[321]

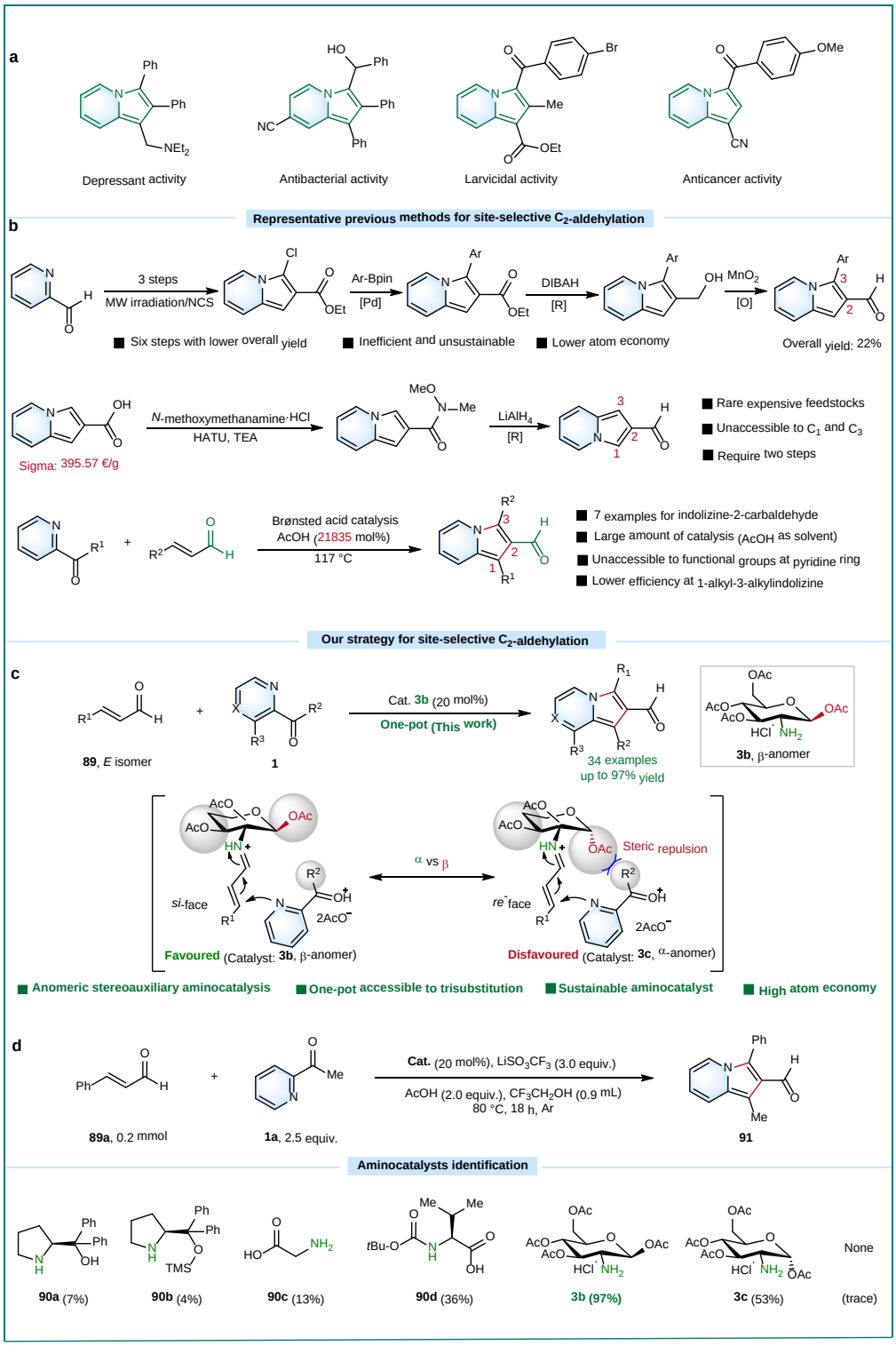


Figure 41 (a) Pharmaceuticals derived from indolizine. (**b)** The representative example of previous approaches for indolizine-carbaldehydes with site-selective C_2-aldehylation. [O] Means oxidation process. [R] Means reduction process. [A] Means amidation process. **(c)** Our strategy: An anomeric

stereoauxiliary organocatalysis by glucosamine enables one-pot site-selective for trisubstituted indolizine-2-carbaldehydes. **(d)** Optimized aminocatalysts for 1,2,3-trisubstituted indolizine-2-carbaldehydes *via* one-pot reaction. NCS means *N*-chlorosuccinimide. DIBAL means diisobutylaluminum hydride.

3.3.2 Optimization studies

We initiated our studies using cinnamaldehyde (**89a**) and 2-acetylpyridine (**1a**) as substrates to evaluate the envisioned aminocatalyzed [3+2] cyclization reaction for the synthesis of desired 1-methyl-3-phenylindolizine-2-carbaldehyde (**4**). At the outset, without catalyst, the reaction was tested with a trace yield of product **4** with a mixture of **89a** (0.2 mmol), **1a** (2.5 equiv.), $LiSO_3CF_3$ (3.0 equiv.) and acetic acid (2.0 equiv.) in CF_3CH_2OH (0.9 mL) for 18 h under Ar gas atmosphere (**Figure 41d**). Then, we examed various aminocatalysts (**Figure 41d**). By using (S)-diphenyl(pyrrolidin-2-yl)methanol (**90a**) and (S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (**90b**) as catalysts, a low yield of product **4** was achieved. Next, diverse sustainable aminocatalysts, including glycine (**90c**), (*tert*-butoxycarbonyl)-L-valine (**90d**), 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranose hydrochlorid (**3b**) and 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrochloride (**3c**), were investigated under the same conditions. As a result, a low yield of **4** was obtained with **90c** and **90d**. Surprisingly, 97% yield of **4** was smoothly delivered by using catalyst **3b**, while **3c** only achieved 53% yield of **4**. Based on all these results, **3b** was taken as the optimal aminocatalyst. In addition to amine-containing catalysts showing the central function for the efficient reaction, acetic acid plays an important role. Without acetic acid, the yield of **4** decreased obviously from 97% to 44%.[243] As well, the amount of $LiSO_3CF_3$ (2 equiv.) and 2-acetylpyridine (1.5 equiv.), reaction time (12 h) and reaction temperature (25 ˚C and 50 ˚C) also affected the yields.

3.3.3 Mechanistic studies

To gain insight into the reaction mechanism, a set of control experiments were conducted (**Figure 42a-42d**). First, under standard condition, catalyst **3b** with β-anomer was examed to smoothly achieve 97% yield of **4**, while catalyst **3c** with α-anomer only yielded 53% of **4** (**Figure 42a** and **42c**)**,** which obviously demonstrates the presence of a strong steric shielding from α-anomer that affects the efficient conversion for the desired product **4**. In the further control groups, **90p** with β-anomer and **90q** with α-anomer were tested under the same conditions (**Figure 42b** and **42d**). Interestingly, product **4** with 51% yield was obtained using **90p** (β-anomer), while **90q** (α-anomer) could only deliver 16% yield. Thus, the imine

reaction pathway *via* aminocatalyst preferentially reacting with α,β-unsaturated aldehydes is reasonable. Besides, the lower yield with **90q** (α-anomer) further provides a strong support for the existing bukyl steric hinderance from acetyl group at C_1-position in **90q**. Therefore, control experiments in **Figure 42** clearly demonstrated that a stereoauxiliary effect favored by β-anomer as well as a steric shielding effect from α-anomer obviously show a tremendous difference during the [3+2] cyclization for the preparation of 1,2,3-trisubstituted indolizine-2-carbaldehydes.

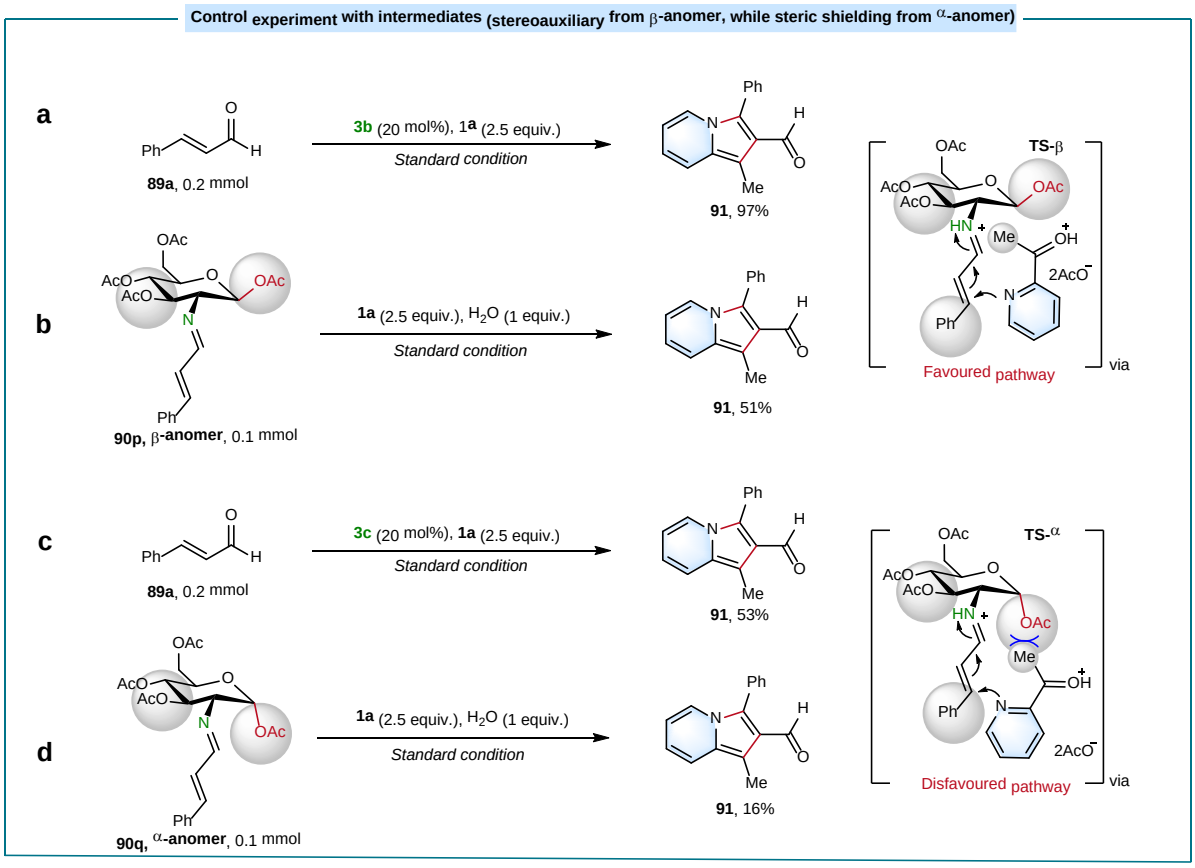


Figure 42 Stereoauxiliary control experiments. **(a)-(d)** Control experiments with intermediates of different anomers: stereoauxiliary from β-anomer, while steric shielding from α-anomer.

Combining all results, the plausible mechanism is proposed (**Figure 43**). First, aminocatalyst **A** reacts with α,β-unsaturated aldehyde **B** to form iminue ion **D**.[180] Then, the 2-acetylpyridine attacks the iminue ion **D** *via* Michael addition reaction to generate an enamine **E**.[163,180] Because there is the bulkyl steric hinder between R^1 and R^2, which could hinder the cyclization of **E**. Thus, an enamine **F** was formed by

the conversion of **E** *via* a rotation. Next, an intermediate **G** forms *via* the intramolecular cyclization reaction in the enamine **F**. Then, an intermediate **H** generates through a dehydration reaction in the intermediate **G**. After that, an intermediate **I** forms from the deprotonation reaction of **H**. Finally, an indolizine **J** generates *via* the hydrolysis reaction of intermedidate **I** and the catalyst **A** regenerates to inter next catalysis cycle.

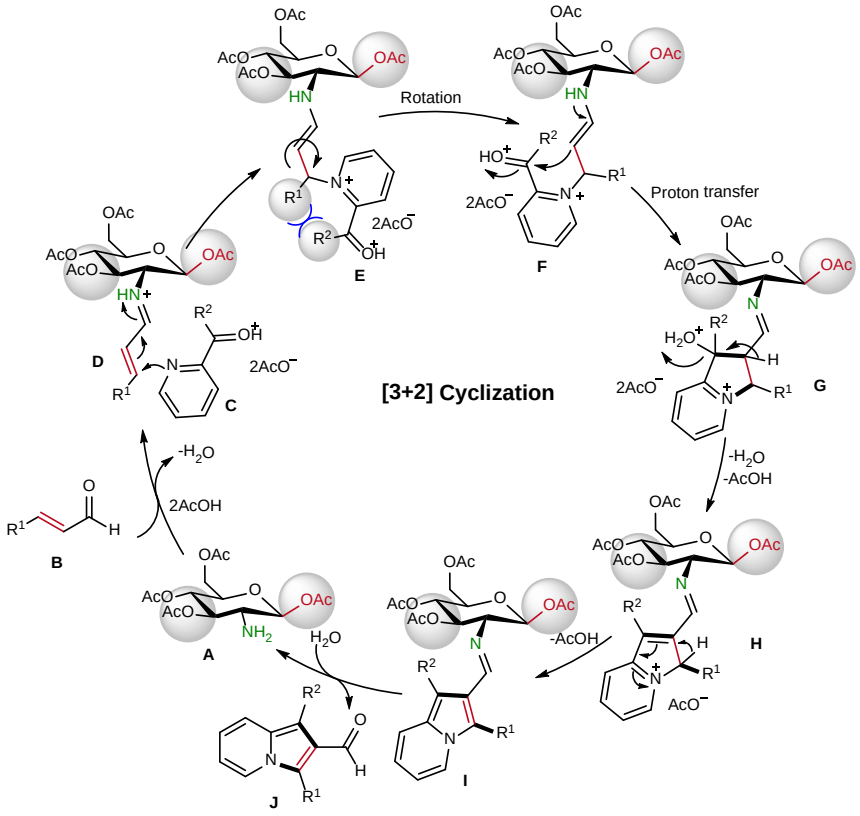


Figure 43 Proposed mechanism.

3.3.4 Scope of substrates

With the optimized reaction conditions in hand, we next probed the scope of various α,β-unsaturated aldehydes using 2-acetypyridine as a representative heteroaryl ketone (**Figure 44a**). A series of α,β-unsaturated aldehydes, including those with electron-donating or -withdrawing groups at different positions (*ortho*, *meta* or *para*), were unprecedentedly delivered to the corresponding products **91**-**100**. An array of valuable products **91**-**95** were efficiently accessed with this aminocatalyzed protocol. Notably,

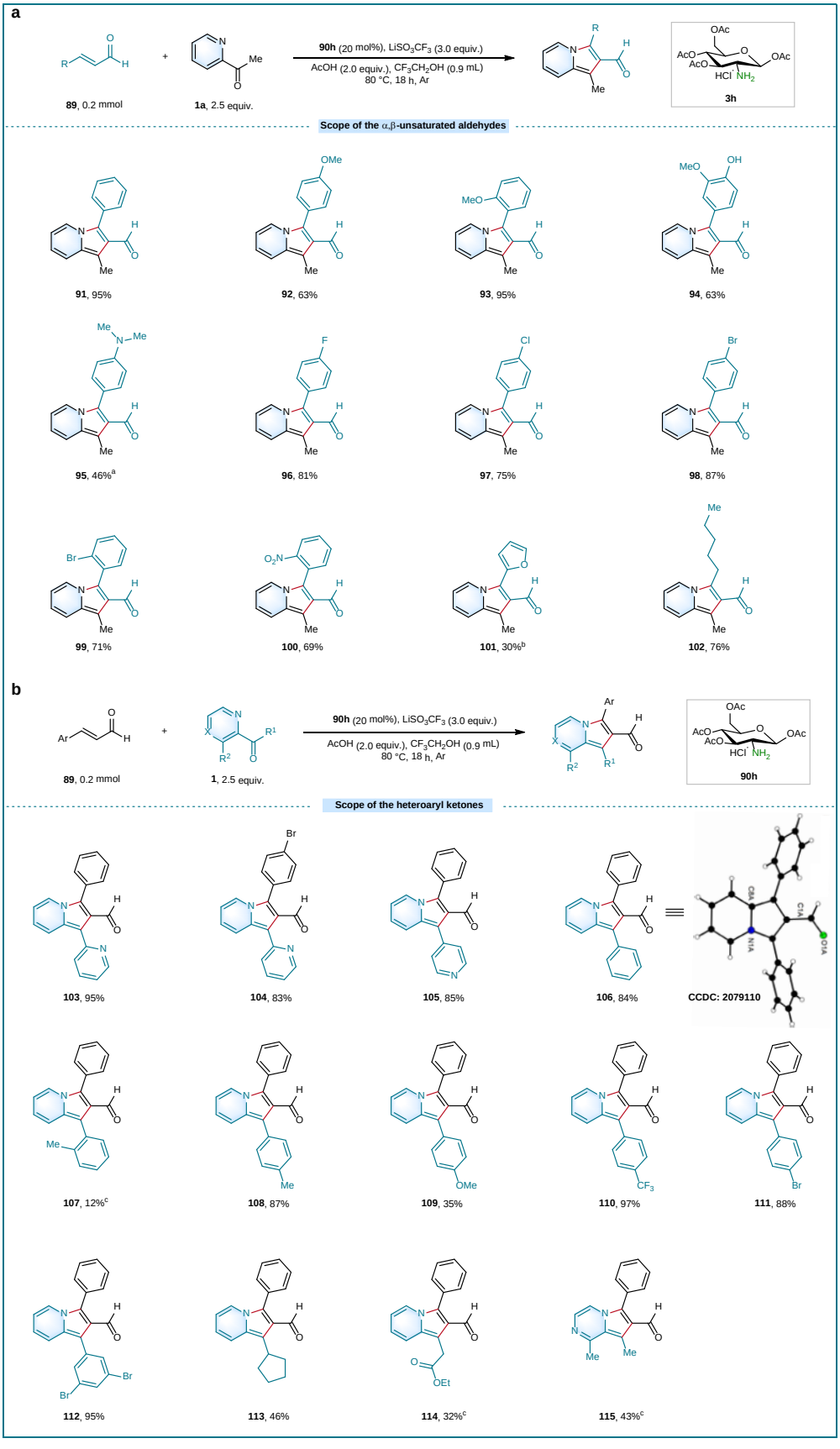

a
89, 0.2 mmol
1a, 2.5 equiv.
90h (20 mol%), LiSO3CF3 (3.0 equiv.)
AcOH (2.0 equiv.), CF3CH2OH (0.9 mL)
80 °C, 18 h, Ar
3h
Scope of the α,β-unsaturated aldehydes
91, 95%
92, 63%
93, 95%
94, 63%
95, 46%a
96, 81%
97, 75%
98, 87%
99, 71%
100, 69%
101, 30%b
102, 76%
b
89, 0.2 mmol
1, 2.5 equiv.
90h (20 mol%), LiSO3CF3 (3.0 equiv.)
AcOH (2.0 equiv.), CF3CH2OH (0.9 mL)
80 °C, 18 h, Ar
90h
Scope of the heteroaryl ketones
103, 95%
104, 83%
105, 85%
106, 84%
CCDC: 2079110
107, 12%c
108, 87%
109, 35%
110, 97%
111, 88%
112, 95%
113, 46%
114, 32%c
115, 43%c

Figure 44 [3+2] annulations for indolizine-2-carbaldehydes. **(a)** Scope of aldehydes. **(b)** Scope of the heteroaryl ketones. [a]Reaction for 36 h in AcOH : CF_3CH_2OH (0.4 : 0.5 mL). [b]AcOH (4.0 equiv.) and reaction for 42 h at r.t. [c]Reaction time 36 h. Yields are those of isolated products.

in our system, a substrate with an electron-donating methoxy group at *ortho* position (**93**, 95%) could even achieve a higher yield than those at *para* position (**92**, 63%). Surprisingly, a native valuble substrate from gliricidia sepium with a hydroxyl group and a methoxy group was smoothly transformed into a value-added indolizine-2-aldehyde with a moderate yield of 63% (**94**). Interestingly, an important substrate for detection of catechins was also tolerant under this method with a 46% yield (**95**). Meanwhile, a variety of valuable funcational groups at diverse positions, such as fluoro (**96**), chloro (**97**), bromo (**98**, **99**), and nitro groups (**100**), were well compatible with these conditions. Particularly, the sensitive (*E*)-3-(furan-2-yl)acrylaldehyde was also tolerated in this protocol and was successfully transformed into desired product (**101**). Moreover, aliphatic α,β-unsaturated aldehyde was also well compatible under the optimal conditions (**102**).

We further explored heteroaryl ketones with cinnamaldehyde as a standard substrate (**Figure 44b**). Di(pyridin-2-yl)methanone and pyridin-2-yl(pyridin-4-yl)methanone were well compatible with the conditions and smoothly achieved 95% (**103**), 83% (**104**) and 85% yield (**105**), respectively. Diverse aromatic pyridine ketones, including those having electron-donating or -withdrawing groups at distinct positions (*ortho*, *meta* or *para*) were well transformed into the corresponding products (**106**-**112**). Various vavluble functional groups at distinct positions (*ortho*, *meta* or *para*), including methoxy (**109**), trifluoromethyl (**110**), bromo (**111**) and dibromo (**112**), were well tolerated undert this condition. The structure of **106** was further confirmed by X-ray crystallographic analysis, and those of other products in **Figure 44** were assigned by analogy. It is worth to note that cyclopentyl(pyridin-2-yl)methanone (**113**) and ethyl 3-oxo-3-(pyridin-2-yl)propanoate (**114**) were also unprecedentedly transformed into valuble 1-alkyl-3-arylindolizine-2-carbaldehydes with the protocol. Surprisingly, 1-(3-methylpyrazin-2-yl)ethan-1- was also compatible with the condition (**115**).

3.3.5 Applications

Indolizines show important biological acticities. To obtain diverse value-added indolizine, it is attractive to introduce a modifiable aldehyde group in an indolzine backbone. Thus, these valuable indolizine-2-carbaldehydes was achieved *via* 6 steps with complex conditions[202] and 2 steps with rare expensive feedstocks (**Figure 45a**).[322] Compared with their protocols *via* carboxylation and reduction for the desired

products, we efficiently achieved a group of value-added 1,2,3-trisubstituted indolizine-2-carbaldehydes *via* totally 2 steps *via* aminocatalyzed [3+2] cyclization reaction. Besides, a group of important bioactive molecules or drugs was investigated in our protocol (**Figure 45b**). Surprisingly, an important fluvastatin intermediate was unprecedentedly accessed by our protocol for the preparation of value-added indolizine-2-carbaldehyde (**116**). As well, (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylaldehyde from gliricidia sepium was also tolerant under the optimal conditions, which led to 3-(4-hydroxy-3-methoxyphenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**117**) with 79% yield. Interestingly, (*E*)-3-(4-(dimethylamino)phenyl) acrylaldehyde that is often used to detect catechins[323] was also smoothly transformed into 3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**118**). Furthermore, the obtained indolizine-2-carbaldehydes could be readily late-stage diversified, thus providing more complex molecules in an efficient manner (**Figure 45c**). Namely, 3-(4-bromophenyl)-1-(pyridin-4-yl)indolizine-2-carbaldehyde (**104**) underwent reduction (**119**), arylation (**120**), acylation (**121**) or dehydration [5+1] annulations (**122**), showcasing the synthetic power of 1,2,3-trisubstituted indolizine-2-carbaldehydes that were assembled *via* our robust stereoaxuliary aminocatalysis. Finally, our anomeric stereoauxiliary aminocatalysis strategy was first time expanded beyond the library of indolizine-2-carbaldehydes to 2-acylindolizines (**123**) and (**124**) (**Figure 45d**).

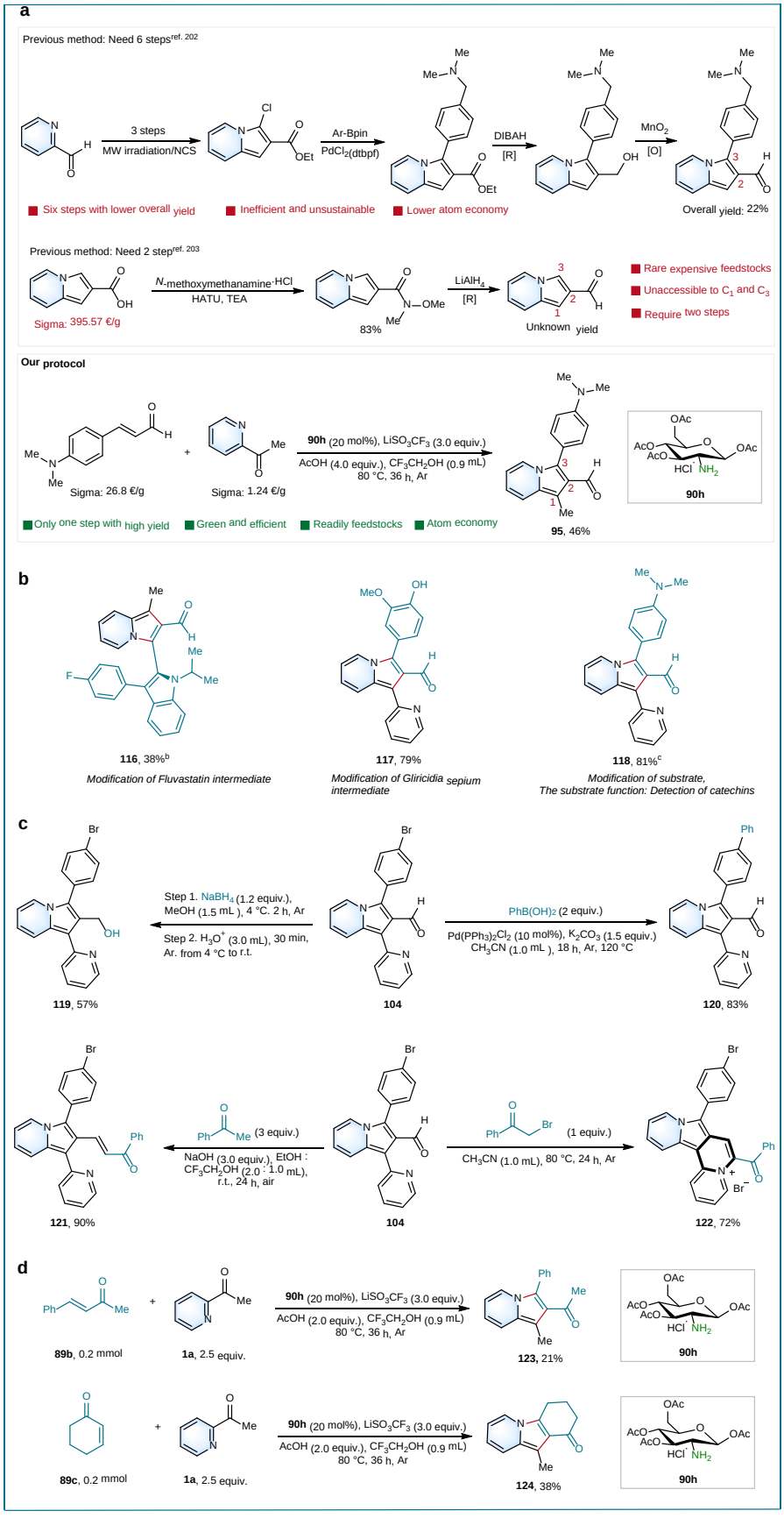

a
Previous method: Need 6 steps[ref. 202]
3 steps
MW irradiation/NCS
Ar-Bpin
PdCl2(dtbpf)
DIBAH
[R]
MnO2
[O]
Six steps with lower overall yield
Inefficient and unsustainable
Lower atom economy
Overall yield: 22%
Previous method: Need 2 step[ref. 203]
N-methoxymethanamine·HCl
HATU, TEA
LiAlH4
[R]
Sigma: 395.57 €/g
83%
Unknown yield
Rare expensive feedstocks
Unaccessible to C1 and C3
Require two steps
Our protocol
Sigma: 26.8 €/g
Sigma: 1.24 €/g
90h (20 mol%), LiSO3CF3 (3.0 equiv.)
AcOH (4.0 equiv.), CF3CH2OH (0.9 mL)
80 °C, 36 h, Ar
95, 46%
90h
Only one step with high yield
Green and efficient
Readily feedstocks
Atom economy
b
116, 38%b
Modification of Fluvastatin intermediate
117, 79%
Modification of Gliricidia sepium intermediate
118, 81%c
Modification of substrate,
The substrate function: Detection of catechins
c
Step 1. NaBH4 (1.2 equiv.),
MeOH (1.5 mL), 4 °C. 2 h, Ar
Step 2. H3O+ (3.0 mL), 30 min,
Ar. from 4 °C to r.t.
PhB(OH)2 (2 equiv.)
Pd(PPh3)2Cl2 (10 mol%), K2CO3 (1.5 equiv.)
CH3CN (1.0 mL), 18 h, Ar, 120 °C
119, 57%
104
120, 83%
NaOH (3.0 equiv.), EtOH :
CF3CH2OH (2.0 : 1.0 mL),
r.t., 24 h, air
(3 equiv.)
CH3CN (1.0 mL), 80 °C, 24 h, Ar
(1 equiv.)
121, 90%
104
122, 72%
d
89b, 0.2 mmol
1a, 2.5 equiv.
90h (20 mol%), LiSO3CF3 (3.0 equiv.)
AcOH (2.0 equiv.), CF3CH2OH (0.9 mL)
80 °C, 36 h, Ar
123, 21%
90h
89c, 0.2 mmol
1a, 2.5 equiv.
90h (20 mol%), LiSO3CF3 (3.0 equiv.)
AcOH (2.0 equiv.), CF3CH2OH (0.9 mL)
80 °C, 36 h, Ar
124, 38%
90h

Figure 45 Synthetic applications. **(a)** Comparison previous protocols with our strategy for indolizine-2-carbaldehyde. **(b)** Late-stage selective modifications of bioactive molecules and drugs. **(c)** Late-stage transformation applications. **(d)** Preliminary expansion of the anomeric stereoauxiliary aminocatalysis strategy beyond α,β-unsaturated aldehyde to enone. [a]Yields are those of isolated products. [b]Reaction for 42 h in AcOH : CF_3CH_2OH (0.45 : 0.45 mL). [c]Reaction for 42 h in AcOH : CF_3CH_2OH (0.4 : 0.5 mL).

4. General conclusions and perspectives

Chitin/chitosan/glucosamine has been increasingly used as a sustainable, environmentally-benign and economically-attractive *N*-containing biomass for organic synthesis of value-added *N*-heterocyclic products. The work in this thesis focuses on developing sustainable strategies for the preparation of value-added imidazo[1,5-a]pyridines and indolizines *via* cyclization reactions from the *N*-containing biomass.

In the first project, we developed a novel α-anomeric stereoauxiliary strategy for the facile preparation of a broad range of imidazo[1,5-a]pyridines, which features the cleavage of C−N bonds of D-glucosamine through a seven-membered ring transition state intermediate and the simultaneous incorporation of amine moieties into valuable imidazo[1,5-a]pyridines (**Figure 46**). 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 hydroxyl group of α-anomer promoted the formation of a seven-membered ring transition state with the acetate anion *via* hydrogen bonds. The ring structure in the α-anomer transition state (TS_{α}) 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 bonds cleavage of aliphatic amine, we believe that this approach with combined anomer-assisting C−N bonds 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 opens a new window for chemical synthesis.

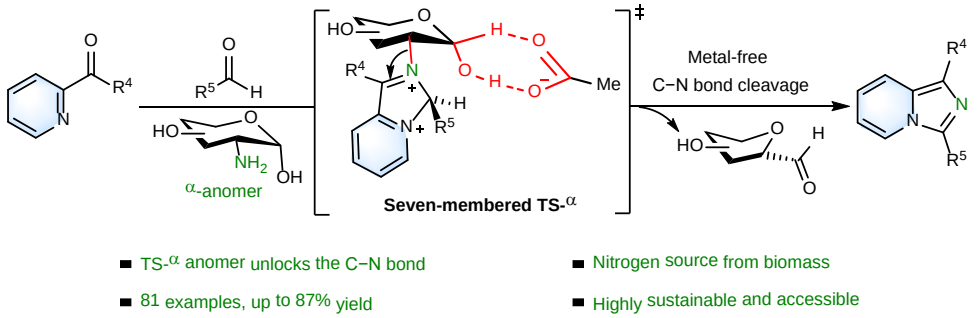


Figure 46 Anomeric stereoauxiliary strategy enables efficient synthesis of wide-ranging imidazo[1,5-a]pyridines

In the second project, we have developed a new strategy for the rapid assembly of NCCs with an ample scope through the direct use of native nitrogen sources from biomass (**Figure 47**). This strategy is achieved through a one-pot conversion approach of chitin/chitosan by cleaving the C–N bonds and simultaneously integrating the nitrogen in the synthesis of a broad range of imidazo[1,5-*a*]pyridines (52 examples) that show diverse potential applications. A broad group of previously inaccessible products including saturated 1-alkylimidazo[1,5-*a*]pyridines is unprecedently synthesized by this protocol. The amine groups of chitin/chitosan backbone are intercepted *via* aldehyde and pyridine ketone assisted with CF_3COOH under metal-free conditions. We believe this approach will initiate research endeavors for the targeted efficient incorporation of nitrogen from biomass for high-value NCCs.

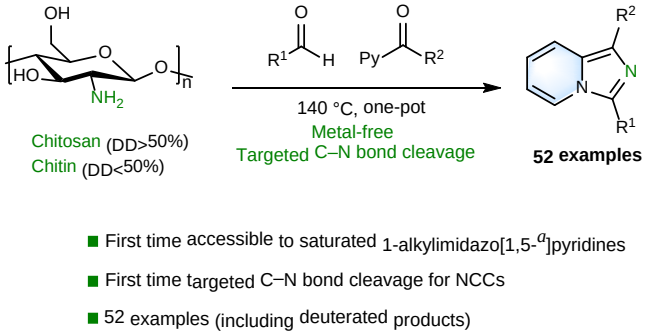


Figure 47 Direct nitrogen interception from chitin/chitosan for imidazo[1,5-a]pyridines.

In the third project, we developed a novel β-anomeric stereoauxiliary glucosamine-catalyzed strategy that first time allows one-pot site-selective C_2-aldehylation for efficient preparation of 1,2,3-trisubstituted indolizine-2-carbaldehydes (**Figure 48**). Utilization of this aminocatalysis strategy with native chiral skeletons for the highly regioselective control, this one-pot approach expands the scope of readily accessible trisubstituted indolizine-2-carbaldehydes relative to existing state-of-the-art methods by multi-steps to introduce carbaldehyde only for mono/di-substituted indolizine-2-carbaldehyde. This method not only enable the efficient C_2-aldehylation of a range of commercial α,β-unsaturated aldehydes and bioactive molecules or drugs, it has been expanded beyond α,β-unsaturated aldehyde to enone. Overall, our anomeric stereoauxiliary catalytic system provides a promising solution towards addressing the challenge associated with indolizine formation with site-selective C_2 aldehylation, on which ongoing work is targeted to apply this strategy towards developing a wider range of catalytic applications.

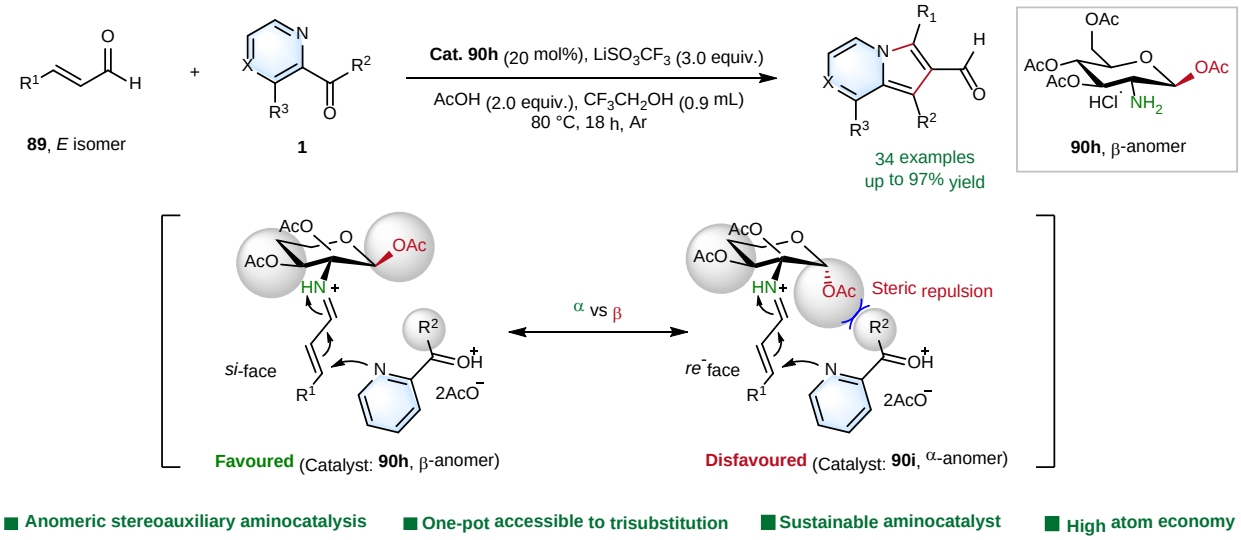


Figure 48 Anomeric stereoauxiliary-organocatalyzed one-pot site-selective C_2-aldehylation for trisubstituted indolizine-2-carbaldehydes

5. Experimental section

5.1 General Remarks

NMR spectra were recorded on Inova 500 or Bruker Avance III 300, Avance III 400 and Acance III HD 500 in the solvent indicated. Chemical shifts are provided in ppm and spectra refer to non-deuterated solvent signal. Yields refer to isolated compounds estimated to be >95% pure as determined by 1H-NMR. Chromatography was carried out on silica gel (40–63 μm). ESI mass spectra were recorded on Bruker Daltonic spectrometers maXis (ESI-QTOF-MS) and micrOTOF (ESI-TOF-MS). GC-MS spectra was performed on an Agilent Technologies chromatograph 7820A GC System and Agilent Technologies 5977E system. GC calibrations were carried out with authentic samples and n-dodecane as an internal standard. FT-IR spectra were recorded on Alpha FT-IR Spectrometer (Bruker, Germany) at room temperature. All samples were measured between 4000 and 500 cm^{-1} with a resolution of 4 cm^{-1} using Platinum ATR and accumulated 24 scans. Melt point were recorded on melting point apparatus, Electrothermal IA 9200. The following starting chemicals were synthesized according to previously described methods: **1d**-**1k**.[324] Unless otherwise specified, the chemicals were obtained commercially and used without further purification. All reactions were performed under an atmosphere of Ar unless specified otherwise.

5.2 General Procedures

General procedure A: Preparation of pyridines ketones substrates

The following starting chemicals were synthesized according to previously described methods: **1d**-**1k**.[324]. A solution of dry THF (15 mL) with bromobenzene (10.0 mmol, 1.00 equiv.) was dropwised into magnesium (12 mmol, 1.2 equiv.) and the mixture solution was stirred in Ar gas in room temperature. After the formation of the Grignard reagent (the color changed to gray), then stopped it. At the same time, picolinonitrile (8 mmol, 0.8 equiv.) was dissolved in dry THF (10 mL), which was dropwised into the former mixture solution of Grignard reagent at 0 ˚C. After the reaction completely, it was quenched by saturated NH_4Cl aqueous solution. The organic layer was separated and extracted twice by CH_2Cl_2. After evaporation, the organic layer was re-dissolved in Et_2O (30 mL) and 6 M HCl (6 mL) was added into the solution. After 30 min, the organic layer was separated. The aqueous layer was basified by saturated $NaHCO_3$ aqueous solution and then extracted three times by CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated in rotary evaporator. The residue was purified by column chromatography with *n*-hexane and ethyl acetate to afford 1b. Other pyridine ketones 1c−1i were prepared with the similar procedures, and characterized by NMR analysis.

General procedure B: Anomeric stereoauxiliary cleavage of the C−N bond of D-glucosamine for the preparation of imidazo[1,5-a]pyridines

General procedure **B1**

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

General procedure **B2**

A mixture of pyridine ketone (0.1 mmol), aldehydes (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h.

Workup: 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 : Et_3N) to give products **4**-**62**. The deuterated products **66**-**86** were synthesized through an analogous procedure to method B1 using AcOH-d_4 : D_2O (0.9 mL : 0.1 mL) as solvent. More experimental details and characterization are available in the Supporting Information.

General procedure C: Direct nitrogen interception from chitin/chitosan for imidazo[1,5-a]pyridines

General procedure **C1**

A mixture of 2-acetylpyridines (0.1 mmol), aldehydes (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight.

General procedure **C2**

A mixture of pyridine ketone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight.

General procedure **C3**

A mixture of pyridine ketone (0.1 mmol), aldehydes (2.0 equiv.) and chitin (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 °C overnight.

General procedure **C4**

A mixture of pyridine ketone (0.1 mmol), aldehydes (4.0 equiv.) and chitin (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 °C overnight.

General procedure **C5**

A mixture of 2-acetylpyridines (0.1 mmol), aldehydes (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried under 100 ºC oven overnight.

Workup: The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by a thermometer. After cooling to room temperature, the reaction mixture was basified up to pH = 7 *via* stad. Na_2CO_3 aqueous solution and then extracted by Et_2O (3×3.0 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration in a rotary evaporator, the crude product was purified with flash chromatography on silica gel (EtOAc: *n*-hexane: Et_3N) to give the desired products.

General procedure D: Anomeric stereoauxiliary-organocatalyzed one-pot site-selective C_2-aldehylation for trisubstituted indolizine-2-carbaldehydes

General procedure **D1**

A mixture of α,β-unsaturated aldehydes or ketones (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h.

General procedure **D2**

A mixture of α,β-unsaturated aldehydes (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3b** (0.04 mmol) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH : AcOH (0.5 : 0.4 mL) were stirred at 80 ºC under Ar atmosphere for 36 h.

General procedure **D3**

A mixture of α,β-unsaturated aldehydes (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (4.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at room temperature under Ar atmosphere for 42 h.

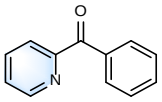
General procedure **D4**

A mixture of α,β-unsaturated aldehydes (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC 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 heating block. 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 *via* stad. Na_2CO_3 aqueous solution, then extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products.

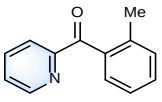
5.3 Characterization Data

5.3.1 Preparation of pyridines ketones substrates



1d

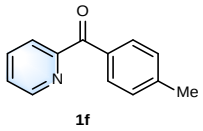
phenyl(pyridin-2-yl)methanone (**1d**): Following the **General procedure A**, work-up gave product **1d** (1189.5 mg, 6.5 mmol, isolated yield 65%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.61 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H), 7.98 – 7.95 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.77 (td, *J* = 8.0, 1.6 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.39 – 7.34 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.64, 154.9, 148.4, 136.9, 136.1, 132.7, 130.8, 128.0, 126.0, 124.4. The compound is known, and the NMR data is in accordance with the previous literature.[325]



1e

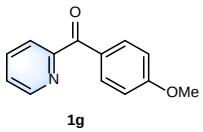
pyridin-2-yl(o-tolyl)methanone (1e): Following the **General procedure A**, work-up gave product **1e** (1004.7 mg, 5.1 mmol, isolated yield 51%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 5.2 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.21 – 7.15 (m, 2H), 2.30 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.4, 155.0, 149.1, 137.8, 137.3, 136.9, 131.1, 130.9,

129.9, 126.4, 125.0, 124.1, 20.4. The compound is known, and the NMR data is in accordance with the previous literature.[326]



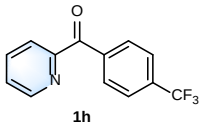
1f

pyridin-2-yl(p-tolyl)methanone (1f): Following the **General procedure A**, work-up gave product **1f** (1241.1 mg, 6.3 mmol, isolated yield 63%) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.4 Hz, 1H), 7.91 – 7.87 (m, 3H), 7.79 – 7.75 (m, 1H), 7.38 – 7.34 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 155.3, 148.4, 143.7, 136.9, 133.5, 131.0, 128.8, 125.9, 124.4, 21.6. The compound is known, and the NMR data is in accordance with the previous literature.[325]



1g

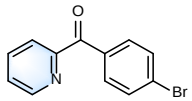
(4-methoxyphenyl)(pyridin-2-yl)methanone (1g): Following the **General procedure A**, work-up gave product **1g** (1597.5 mg, 7.5 mmol, isolated yield 75%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.4 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.38 (m, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.3, 163.5, 155.8, 148.3, 137.0, 133.5, 129.0, 125.8, 124.5, 113.5, 55.5. The compound is known, and the NMR data is in accordance with the previous literature.[325]



1h

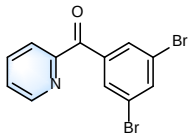
pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone (1h): Following the **General procedure A**, work-up gave product **1h** (1129.5 mg, 4.5 mmol, isolated yield 45%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.64 – 8.62 (m, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.84 (td, *J* = 8.0, 1.6 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.43 (ddd, *J* = 7.6 Hz, 4.8, 1.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.7, 154.1, 148.6, 139.3 (q, $^{4}J_{C\text{-}F}$ = 1.2 Hz), 137.25 , 133.85 (q, $^{2}J_{C\text{-}F}$ = 32.6 Hz), 131.2, 126.7, 125.0 (q,

$^{3}J_{C\text{-}F}$ = 3.8 Hz), 124.7, 123.7 (q, $^{1}J_{C\text{-}F}$ = 270.9 Hz), 115.4. ^{19}F NMR (375 MHz, $CDCl_3$): δ -63.13. The compound is known, and the NMR data is in accordance with the previous literature.[327]



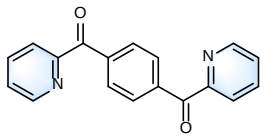
1i

pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone (1i): Following the **General procedure A**, work-up gave product **1i** (1357.2 mg, 5.2 mmol, isolated yield 52%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 5.5 Hz, 1H), 7.98 – 7.88 (m, 3H), 7.83 – 7.79 (m, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.41 – 7.38 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.5, 154.5, 148.4, 137.1, 134.9, 132.5, 131.3, 128.1, 126.4, 124.6. **ESI-HRMS**: *m/z* calcd. for $C_{12}H_8BrNO$ $[M+H]^+$: 261.9868, found 263.9846. The compound is known, and the NMR data is in accordance with the previous literature.[328]



1j

(3,5-dibromophenyl)(pyridin-2-yl)methanone (1j): Following the **General procedure A**, work-up gave product **1j** (1186.2 mg, 3.5 mmol, isolated yield 35%) as a white green solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67 – 8.66 (m, 1H), 8.11 (s, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.80 (s, 1H), 7.48 – 7.44 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.6, 153.7, 148.7, 139.2, 137.8, 137.3, 132.6, 126.9, 124.8, 122.7. **ESI-HRMS**: *m/z* calcd. for $C_{12}H_7Br_2NO$ $[M+H]^+$: 339.8973, found 339.8969.

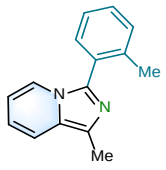


1k

1,4-phenylenebis(pyridin-2-ylmethanone) (1k): Following the **General procedure A**, work-up gave product **1k** (316.8 mg, 1.1 mmol, isolated yield 11%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67 – 8.65 (m, 2H), 8.09 (d, *J* = 0.8 Hz, 4H), 8.02 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.88 – 7.83 (m, 2H), 7.46 – 7.43 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 154.4, 148.6, 139.4, 137.1, 130.5, 126.5, 124.6.

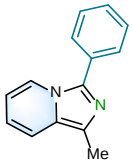
ESI-HRMS: *m/z* calcd. for $C_{18}H_{12}N_2O_2$ $[M+H]^+$: 289.0977, found 289.0972. The compound is known, and the NMR data is in accordance with the previous literature.[328]

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



4

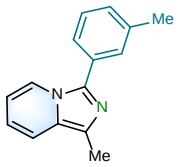
Methyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **4** (14.4 mg, 0.065 mmol, isolated yield 65%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3066, 2924, 2852, 1671, 1630, 1605, 1554, 1515, 1451, 1412, 1362, 1319, 1247, 1140, 1107, 1072, 1037, 1006, 940, 865, 808, 773, 734, 694, 657, 596, 575, 546, 492, 447, 418. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.17 (m, 5H), 6.53 – 6.48 (m, 1H), 6.35 – 6.30 (m, 1H), 2.49 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.1, 136.2, 130.6, 130.4, 129.5, 129.1, 127.9, 126.7, 125.9, 121.2, 118.0, 116.6, 112.2, 19.6, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1230.



5

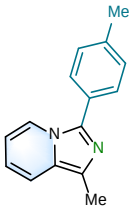
1-methyl-3-phenylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), benzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **5** (17.3 mg, 0.083 mmol, isolated yield 83%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3056, 2918, 2850, 1659, 1603, 1572, 1517, 1451, 1409, 1362, 1257, 1076, 1024, 1004, 942, 915, 775, 738, 688, 616, 480, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.30 (m, 2H), 6.56 – 6.52 (m, 1H), 6.41 (t, *J* = 6.8 Hz, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ

136.5, 130.3, 128.9, 128.4, 127.9, 127.7, 121.1, 118.3, 117.0, 112.9, 12.5. The compound is known, and the NMR data is in accordance with the previous literature.[329]



6

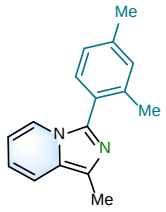
1-methyl-3-(m-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **6** (16.0 mg, 0.072 mmol, isolated yield 72%) as a yellow solid. **Mp**: 105−107 ˚C. **FT-IR**: *v* (cm^{-1}): 2963, 2920, 2852, 1659, 1607, 1583, 1519, 1463, 1432, 1366, 1261, 1201, 1094, 1026, 913, 882, 793, 738, 723, 696, 618, 548, 521, 439, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.56 – 6.52 (m, 1H), 6.41 (t, *J* = 6.8 Hz, 1H), 2.48 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.8, 136.7, 132.7, 130.2, 129.2, 128.7, 128.6, 127.9, 124.5, 121.2, 118.3, 117.0, 112.8, 21.4, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1231.



7

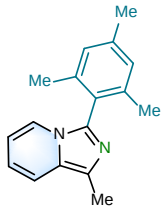
1-methyl-3-(p-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **7** (17.3 mg, 0.078 mmol, isolated yield 78%) as a yellow solid. **Mp**: 62−64 ˚C. FT-IR: *v* (cm^{-1}): 2914, 2852, 1661, 1611, 1570, 1529, 1492, 1405, 1360, 1259, 1183, 1111, 1076, 1034, 1020, 946, 820, 732, 690, 579, 492, 427. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 9.1 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.52 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.40 – 6.37 (m, 1H), 2.48 (s, 3H),

2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.3, 136.7, 129.6, 128.6, 127.7, 127.6, 127.5, 121.2, 118.3, 116.8, 112.6, 21.4, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1234.



8

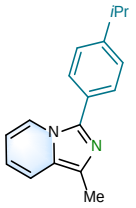
3-(2,4-dimethylphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2,3-dimethylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **8** (16.0 mg, 0.068 mmol, isolated yield 68%) as a brown solid. **Mp**: 81−83 ˚C. **FT-IR**: *v* (cm^{-1}): 2920, 2856, 1663, 1616, 1447, 1414, 1362, 1234, 1152, 1109, 1072, 1032, 1001, 950, 878, 818, 740, 696, 591, 546, 424. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 6.8 Hz, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.08 (s, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.55 – 6.51 (m, 1H), 6.36 – 6.33 (m, 1H), 2.48 (s, 3H), 2.31 (s, 3H), 2.08 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.1, 137.9, 136.3, 132.0, 131.4, 130.4, 127.6, 126.7, 126.4, 121.3, 118.1, 116.7, 112.2, 21.3, 19.6, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{16}N_2$ $[M+H]^+$: 237.1392, found 237.1386.



9

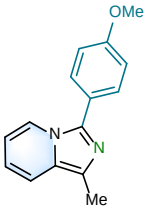
3-mesityl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2,4,6-trimethylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **9** (14.0 mg, 0.056 mmol, isolated yield 56%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2924, 2852, 1669, 1630, 1611, 1574, 1550, 1519, 1459, 1442, 1412, 1377, 1360, 1319, 1189, 1119, 1072, 1032, 1001, 925, 849, 773, 738, 699, 596, 560, 544, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 9.2 Hz, 1H),

7.14 –7.12 (m, 1H), 6.88 (s, 2H), 6.52 – 6.48 (m, 1H), 6.32 – 6.28 (m, 1H), 2.50 (s, 3H), 2.27 (s, 3H), 1.88 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.1, 139.1, 135.5, 128.3, 127.5, 126.2, 126.2, 120.9, 118.0, 116.3, 112.0, 21.2, 19.5, 12.7. **ESI-HRMS**: m/z calcd. for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1548, found 251.1542.



10

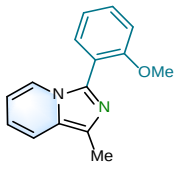
3-(4-isopropylphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-isopropylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **10** (17.8 mg, 0.071 mmol, isolated yield 71%) as a brown solid. **Mp**: 61−63 ˚C. **FT-IR**: *v* (cm^{-1}): 2961, 2922, 2864, 1671, 1607, 1527, 1457, 1414, 1383, 1362, 1306, 1255, 1199, 1175, 1127, 1076, 1053, 1018, 948, 835, 797, 777, 736, 717, 690, 637, 593, 532, 414. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.60 (m, 2H), 7.32 – 7.27 (m, 3H), 6.55 – 6.51 (m, 1H), 6.41 – 6.37 (m, 1H), 2.93 – 2.86 (m, 1H), 2.48 (s, 3H), 1.22 (dd, *J* = 6.8, 1.2 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.4, 136.5, 128.3, 127.8, 127.7, 127.5, 127.0, 121.2, 118.3, 117.0, 112.8, 34.0, 23.9, 12.3. **ESI-HRMS**: m/z calcd. for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1548, found 251.1542.



11

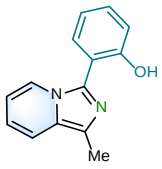
3-(4-methoxyphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-methoxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **11** (18.6 mg, 0.078 mmol, isolated yield 78%) as a yellow solid. **Mp**: 61−63 ˚C. **FT-IR**: *v* (cm^{-1}):

2961, 2922, 2838, 1661, 1605, 1498, 1459, 1362, 1300, 1251, 1173, 1107, 1022, 835, 797, 734, 690, 581, 515. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.29 – 7.26 (m, 1H), 6.96 – 6.93 (m, 2H), 6.51 – 6.47 (m, 1H), 6.38 – 6.34 (m, 1H), 3.78 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.7, 136.5, 129.2, 128.3, 127.5, 122.9, 121.0, 118.3, 116.6, 114.3, 112.6, 55.3, 12.4. **ESI-HRMS**: m/z calcd. for $C_{15}H_{14}N_2O$ $[M+H]^+$: 239.1184, found 239.1181.



12

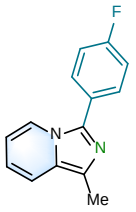
3-(2-methoxyphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-methoxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **12** (17.6 mg, 0.074 mmol, isolated yield 74%) as a yellow solid. **Mp**: 55−57 ˚C. **FT-IR**: *v* (cm^{-1}): 2916, 2848, 1735, 1663, 1601, 1581, 1512, 1467, 1436, 1418, 1362, 1238, 1179, 1160, 1109, 1045, 1018, 940, 797, 732, 690, 651, 583, 565, 534, 490, 449, 424. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.36 – 7.27 (m, 2H), 7.01 – 6.97 (m, 1H), 6.92 (d, *J* = 8.00 Hz, 1H), 6.54 – 6.50 (m, 1H), 6.35 – 6.31 (m, 1H), 3.70 (s, 3H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.1, 134.3, 132.3, 130.3, 128.1, 127.5, 122.8, 121.0, 119.3, 117.6, 116.6, 111.4, 111.0, 55.4, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_4N_2O$ $[M+H]^+$: 239.0402, found 239.0397.



13

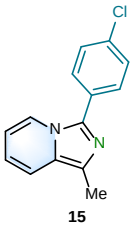
2-(1-methylimidazo[1,5-a]pyridin-3-yl)phenol: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-hydroxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **13** (14.6 mg, 0.065 mmol, isolated yield 65%) as a white solid. **Mp**: 137−138 ˚C. **FT-IR**: *v* (cm^{-1}): 2922, 2856, 1735, 1653, 1609, 1583, 1519, 1469, 1436, 1381, 1364, 1290, 1253, 1236, 1181, 1156, 1102, 1076, 1037, 1012, 933, 812, 752, 734, 690, 655, 596, 577, 548, 534, 455, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ

8.35 (d, *J* = 7.2 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.37 – 7.34 (m, 1H), 7.20 – 7.17 (m, 1H), 7.08 – 7.05 (m, 1H), 6.92 – 6.88 (m, 1H), 6.64 – 6.60 (m, 1H), 6.54 – 6.50 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.3, 134.3, 129.4, 127.2, 127.0, 123.8, 121.9, 118.8, 118.6, 117.7, 117.7, 114.4, 113.7, 12.3. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{12}N_2O_1$ $[M+H]^+$: 225.1028, found 225.1028.



14

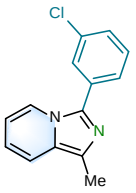
3-(4-fluorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-fluorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **14** (18.1 mg, 0.080 mmol, isolated yield 80%) as a yellow solid. **Mp**: 80−82 ˚C. **FT-IR**: *ν* (cm^{-1}): 2963, 2920, 2852, 1665, 1603, 1496, 1412, 1368, 1257, 1222, 1156, 1092, 1012, 837, 791, 738, 688, 577, 507. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.75 – 7.70 (m, 2H), 7.38 – 7.34 (m, 1H), 7.17 – 7.11 (m, 2H), 6.69 – 6.60 (m, 1H), 6.57 – 6.52 (m, 1H), 2.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.0 (d, $^1J_{C\text{-}F}$ = 248.6 Hz), 134.4, 129.9 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 127.6, 127.14, 124.4 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 120.8, 118.4, 118.3, 116.3 (d, $^2J_{C\text{-}F}$ = 21.9 Hz), 114.4, 11.6. **^{19}F NMR** (375 MHz, $CDCl_3$): δ -110.68. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}FN_2$ $[M+H]^+$: 227.0985, found 227.0980.



15

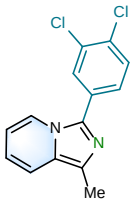
3-(4-chlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-chlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **15** (19.8 mg, 0.082 mmol, isolated yield 82%) as a yellow solid. **Mp**: 63−65 ˚C. **FT-IR**: *ν* (cm^{-1}): 2959, 2926, 2852, 2096, 1896, 1663, 1589, 1504, 1405, 1257, 1086, 1010, 797, 736, 709, 686, 573, 544, 499,

484, 424. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 1H), 6.58 – 6.55 (m, 1H), 6.46 – 6.43 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 135.3, 134.1, 129.2, 129.1, 128.9, 128.8, 128.2, 120.9, 118.4, 117.2, 113.2, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}ClN_2$ $[M+H]^+$: 243.0689, found 243.0687.



16

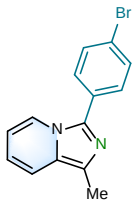
3-(3-chlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3-chlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **16** (18.2 mg, 0.075 mmol, isolated yield 75%) as a brown solid. **Mp**: 70−72 ˚C. **FT-IR**: *v* (cm^{-1}): 2965, 2918, 2850, 1653, 1560, 1407, 1257, 1069, 1010, 795, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.71 (s, 1H), 7.60 – 7.58 (m, 1H), 7.35 – 7.28 (m, 3H), 6.61 – 6.57 (m, 1H), 6.49 – 6.46 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 132.1, 131.1, 130.2, 129.3, 128.4, 128.3, 127.6, 125.6, 121.0, 118.5, 117.4, 113.4, 12.5. **ESI-HRMS**: m/z calcd. for $C_{14}H_{11}ClN_2$ $[M+H]^+$: 243.0689, found 243.0685.



17

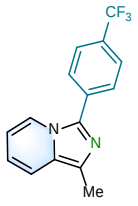
3-(3,4-dichlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3,4-dichlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **17** (17.1 mg, 0.062 mmol, isolated yield 62%) as a yellow solid. **Mp**: 117−118 ˚C. **FT-IR**: *v* (cm^{-1}): 2959, 1665, 1628, 1589, 1550, 1498, 1440, 1414, 1395, 1257, 1078, 1010, 872, 797, 732, 696, 666, 521, 436. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H), 7.57 – 7.54 (m, 1H), 7.49 – 7.46 (m, 1H), 7.35 – 7.32 (m, 1H), 6.62 – 6.57 (m, 1H), 6.51 – 6.47 (m, 1H), 2.48 (s, 3H). **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 134.0, 133.2, 132.0, 130.8, 130.4, 129.6, 129.2, 128.6, 126.4, 120.8, 118.5, 117.5, 113.6, 12.5. **ESI-HRMS**: m/z calcd. for $C_{14}H_{10}Cl_2N_2$ $[M+H]^+$: 277.0299, found 277.0295.



18

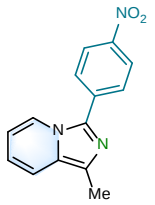
3-(4-bromophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-bromobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **18** (22.6 mg, 0.079 mmol, isolated yield 79%) as a yellow solid. **Mp**: 90−92 ˚C. **FT-IR**: *v* (cm^{-1}): 2920, 2850, 1659, 1589, 1506, 1459, 1401, 1362, 1255, 1230, 1105, 1069, 1008, 942, 826, 734, 684, 492, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.54 (m, 4H), 7.33 (d, *J* = 8.8 Hz, 1H), 6.58 – 6.55 (m, 1H), 6.46 – 6.43 (m, 1H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.4, 132.1, 129.4, 129.3, 129.1, 128.3, 122.2, 120.9, 118.5, 117.2, 113.2, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}BrN_2$ $[M+H]^+$: 287.0184, found 287.0181.



19

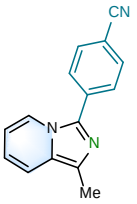
1-methyl-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-(trifluoromethyl)benzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **19** (23.7 mg, 0.086 mmol, isolated yield 86 %) as a yellow solid. **Mp**: 73−74 ˚C. **FT-IR**: *v* (cm^{-1}): 3062, 2918, 2858, 1675, 1618, 1521, 1418, 1321, 1255, 1166, 1111, 1065, 1012, 843, 802, 738, 684, 604, 499, 437. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.34 (m, 1H), 6.62 – 6.59 (m, 1H), 6.51 – 6.47 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.9, 133.9 (q, $^4J_{C\text{-}F}$ = 1.1 Hz), 129.8 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 129.8, 128.7, 127.6, 125.9 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 270.3 Hz), 120.9, 118.5, 117.6, 113.6, 12.6.

^{19}F NMR (375 MHz, $CDCl_3$): δ -62.60. **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}F_3N_2$ $[M+H]^+$: 277.0953, found 277.0950.



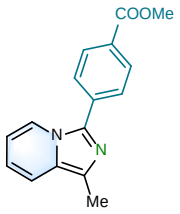
20

1-methyl-3-(4-nitrophenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-nitrobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **20** (20.5 mg, 0.081 mmol, isolated yield 81%) as a red solid. **Mp**: 142−144 ˚C. **FT-IR**: *v* (cm^{-1}): 2912, 1677, 1628, 1589, 1496, 1447, 1424, 1309, 1257, 1173, 1107, 1069, 1016, 948, 847, 814, 750, 738, 692, 676, 546, 523, 490, 476, 433, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.29 – 8.26 (m, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.95 – 7.92 (m, 2H), 7.41 (d, *J* = 9.1 Hz, 1H), 6.71 – 6.67 (m, 1H), 6.61 – 6.57 (m, 1H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 146.7, 136.5, 134.0, 131.0, 129.6, 127.3, 124.4, 121.0, 118.7, 118.4, 114.3, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}N_3O_2$ $[M+H]^+$: 254.0930, found 254.0928.



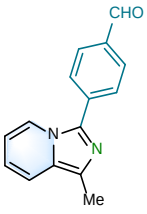
21

4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzonitrile: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-formylbenzonitrile (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **21** (16.8 mg, 0.072 mmol, isolated yield 72%) as a yellow solid. **Mp**: 89−91 ˚C. **FT-IR**: *v* (cm^{-1}): 2957, 2910, 2844, 1655, 1605, 1552, 1510, 1395, 1257, 1082, 1010, 857, 789, 734, 686, 519. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.6 Hz, 1H), 7.87 – 7.84 (m, 2H), 7.69 – 7.67 (m, 2H), 7.38 (d, *J* = 9.2 Hz, 1H), 6.65 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.56 – 6.52 (m, 1H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.6, 134.3, 132.7, 130.5, 129.2, 127.5, 120.9, 118.7, 118.7, 118.2, 114.1, 111.1, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}N_3$ $[M+H]^+$: 234.1031, found 234.1030.



22

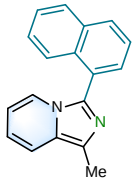
methyl 4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzoate: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), methy-4-formylbenzoate (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **22** (12.0 mg, 0.043 mmol, isolated yield 43%) as a brown solid. **Mp**: 92−94 ˚C. **FT-IR**: *v* (cm^{-1}): 2953, 2920, 2850, 1717, 1661, 1607, 1434, 1269, 1177, 1102, 1016, 960, 859, 797, 775, 736, 702, 568, 540, 490, 420. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.0, 6.0 Hz, 1H), 6.52 – 6.49 (m, 1H), 3.87 (s, 3H), 2.49 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.6, 134.5, 130.2, 129.8, 129.4, 128.8, 127.4, 127.1, 121.1, 118.5, 117.8, 52.2, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{14}N_2O_2$ $[M+H]^+$: 267.1134, found 267.1132.



23

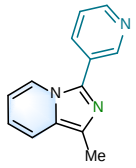
4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzaldehyde: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), terephthalaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **23** (16.0 mg, 0.068 mmol, isolated yield 68%) as a yellow solid. **Mp**: 313−315 ˚C. **FT-IR**: *v* (cm^{-1}): 2914, 1698, 1599, 1381, 1012, 795, 670. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.21 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.92 – 7.92 (m, 4H), 7.37 (dd, *J* = 9.2, 1.2 Hz, 1H), 6.66 – 6.62 (m, 1H), 6.55 – 6.51 (m, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.5, 136.0, 135.3, 135.0, 130.4, 130.3, 129.1, 127.4,

121.2, 118.6, 118.0, 113.8, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1028, found 237.1026.



24

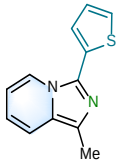
-methyl-3-(naphthalen-1-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 1-naphthaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **24** (15.2 mg, 0.059 mmol, isolated yield 59%) as a brown solid. **Mp**: 91−93 ˚C. **FT-IR**: *v* (cm^{-1}): 3054, 2918, 2854, 1659, 1585, 1513, 1461, 1416, 1366, 1249, 1212, 1142, 1092, 1020, 995, 933, 865, 804, 773, 738, 694, 645, 577, 532, 503, 412. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 – 7.95 (m, 2H), 7.76 – 7.73 (m, 2H), 7.63 – 7.58 (m, 2H), 7.57 – 7.53 (m, 1H), 7.50 – 7.46 (m, 2H), 6.69 – 6.65 (m, 1H), 6.44 – 6.40 (m, 1H), 2.67 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.3, 134.0, 131.8, 129.6, 128.6, 128.6, 128.5, 127.6, 127.5, 126.9, 126.2, 125.7, 125.4, 121.6, 118.2, 117.0, 112.3, 12.7. **ESI-HRMS**: m/z calcd. for $C_{18}H_{14}N_2$ $[M+H]^+$: 259.1235, found 259.1233.



25

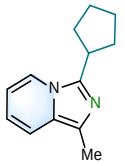
1-methyl-3-(pyridin-3-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), nicotinaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **25** (8.8 mg, 0.042 mmol, isolated yield 42%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3035, 2922, 2858, 1675, 1630, 1587, 1568, 1510, 1496, 1420, 1362, 1327, 1300, 1255, 1179, 1150, 1123, 1078, 1022, 1006, 944, 808, 736, 709, 688, 616, 546, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.99 (d, *J* = 2.0 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 8.05 – 8.03 (m, 1H), 7.38 – 7.35 (m, 2H), 6.61 (dd, *J* = 9.1, 6.3 Hz,

1H), 6.52 – 6.48 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.1, 148.2, 135.1, 133.4, 129.8, 128.6, 126.8, 123.8, 120.7, 118.5, 117.6, 113.6, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{11}N_3$ $[M+H]^+$: 210.1031, found 210.1027.



26

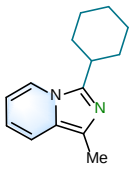
1-methyl-3-(thiophen-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), thiophene-2-carbaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **26** (11.8 mg, 0.055 mmol, isolated yield 55%) as a brown solid. **Mp**: 79−81 ˚C. **FT-IR**: *v* (cm^{-1}): 3074, 2959, 2920, 2854, 1735, 1649, 1603, 1513, 1463, 1401, 1364, 1253, 1037, 909, 843, 804, 682, 416. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 – 8.16 (m, 1H), 7.42 – 7.40 (m, 1H), 7.35 – 7.30 (m, 2H), 7.10 (ddd, *J* = 4.8, 3.6, 1.2 Hz, 1H), 6.60 – 6.50 (m, 2H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 132.7, 131.3, 129.3, 128.2, 127.6, 125.4, 124.0, 121.5, 118.4, 117.0, 113.5, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{12}H_{10}N_2S$ $[M+H]^+$: 215.0643, found 215.0641.



27

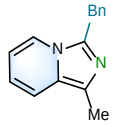
3-cyclopentyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), cyclopentanecarbaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **27** (16.2 mg, 0.081 mmol, isolated yield 81%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 2945, 2864, 1667, 1504, 1449, 1434, 1339, 1314, 1284, 1241, 1199, 1158, 1094, 993, 938, 795, 732, 692, 620, 587, 422, 402. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 9.6 Hz, 1H), 6.44 – 6.39 (m, 1H), 6.35 – 6.31 (m, 1H), 3.25 (p, *J* = 8.3 Hz, 1H), 2.40 (s, 3H), 2.08 – 2.01 (m, 2H), 1.96 – 1.89 (m, 2H), 1.80 – 1.75 (m, 2H), 1.64 – 1.61 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.5, 126.6, 126.0, 120.4, 118.1,

115.6, 111.5, 36.6, 30.8, 25.5, 12.4. **ESI-HRMS**: m/z calcd. for $C_{13}H_{16}N_2$ $[M+H]^+$: 201.1392, found 201.1384.



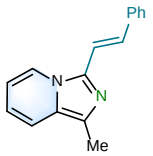
28

3-cyclohexyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), cyclohexanecarbaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **28** (17.8 mg, 0.083 mmol, isolated yield 83%) as a white solid. **Mp**: 92−94 ˚C. **FT-IR**: *v* (cm^{-1}): 2920, 2850, 1663, 1591, 1480, 1445, 1259, 1170, 1090, 1018, 890, 795, 742, 694, 643,542, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 6.44 – 6.40 (m, 1H), 6.35 – 6.32 (m, 1H), 2.88 – 2.80 (m, 1H), 2.41 (s, 3H), 1.95 – 1.90 (m, 2H), 1.85 – 1.80 (m, 2H), 1.74 – 1.64 (m, 3H), 1.41 – 1.25 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.4, 126.4, 126.2, 120.2, 118.3, 115.6, 111.5, 35.7, 30.8, 26.4, 26.0, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{18}N_2$ $[M+H]^+$: 215.1548, found 215.1546.



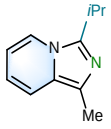
29

3-benzyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-phenylacetaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **29** (9.1 mg, 0.041 mmol, isolated yield 41%) as a brown solid. **Mp**: 89−91 ˚C. **FT-IR**: *v* (cm^{-1}): 3054, 3029, 2961, 2926, 1663, 1599, 1494, 1453, 1370, 1261, 1222, 1156, 1074, 1030, 800, 746, 696, 565, 460. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.18 (m, 3H), 7.15 – 7.13 (m, 1H), 7.11 – 7.09 (m, 2H), 6.47 – 6.43 (m, 1H), 6.30 – 6.26 (m, 1H), 4.31 (s, 2H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.6, 135.2, 129.8, 128.8, 128.6, 128.2, 126.7, 120.5, 118.2, 116.1, 112.1, 33.5, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1231.



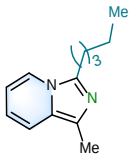
30

(*E*)-1-methyl-3-styrylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), cinnamaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **30** (3.3 mg, 0.014 mmol, isolated yield 14%) as a brown solid. **Mp**: 110−112 ˚C. **FT-IR**: *v* (cm^{-1}): 3031, 2918, 2848, 2089, 1659, 1628, 1597, 1548, 1513, 1492, 1449, 1412, 1374, 1333, 1261, 1241, 1197, 1129, 1094, 1072, 1026, 954, 795, 750, 696, 550, 495, 416. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.59 – 6.51 (m, 2H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.0, 134.9, 130.0, 128.8, 127.9, 127.9, 126.6, 120.5, 118.5, 117.3, 113.4, 111.7, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{14}N_2$ $[M+H]^+$: 235.1235, found 235.1229.



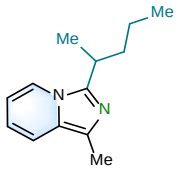
31

3-isopropyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), isobutyraldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **31** (9.2 mg, 0.053 mmol, isolated yield 53%) as a brown solid. **Mp**: 94−95 ˚C. **FT-IR**: *v* (cm^{-1}): 2959, 2928, 2866, 1659, 1587, 1455, 1368, 1199, 1175, 1125, 1096, 800, 740, 717, 694, 620, 587, 422. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 6.44 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.38 – 6.33 (m, 1H), 3.20 (hept, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.35 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.7, 126.4, 120.2, 118.3, 115.9, 112.0, 25.9, 20.5, 12.3. **ESI-HRMS**: *m/z* calcd. for $C_{11}H_{14}N_2$ $[M+H]^+$: 175.1235, found 175.1224.



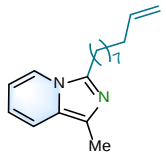
32

1-methyl-3-pentylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), hexanal (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. work-up gave product **32** (16.6 mg, 0.082 mmol, isolated yield 82%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3342, 3186, 2957, 2928, 2858, 1665, 1500, 1463, 1377, 1228, 1181, 1092, 997, 859, 795, 732, 694, 620, 418. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 10.0 Hz, 1H), 6.43 – 6.40 (m, 1H), 6.35 – 6.32 (m, 1H), 2.83 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.72 (p, *J* = 7.2 Hz, 2H), 1.31 – 1.27 (m, 4H), 0.82 (t, *J* = 6.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.3, 126.3, 126.3, 120.2, 118.1, 115.5, 111.7, 31.6, 26.9, 26.5, 22.3, 13.9, 12.3. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{18}N_2$ $[M+H]^+$: 203.1548, found 203.1543.



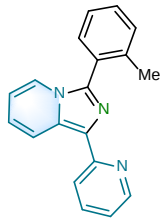
33

1-methyl-3-(pentan-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylpentanal (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **33** (17.0 mg, 0.084 mmol, isolated yield 84%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3334, 3180, 2963, 2928, 2875, 1665, 1461, 1459, 1374, 1337, 1282, 1238, 1188, 1154, 1094, 1055, 997, 868, 787, 738, 694, 622, 416. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 9.2 Hz, 1H), 6.43 – 6.39 (m, 1H), 6.34 – 6.31 (m, 1H), 3.07 (h, *J* = 7.0 Hz, 1H), 2.40 (s, 3H), 1.85 – 1.76 (m, 1H), 1.65 – 1.56 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.27 – 1.17 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 141.3, 126.4, 126.1, 120.1, 118.2, 115.5, 111.7, 37.5, 30.9, 20.6, 18.6, 13.9, 12.3. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{18}N_2$ $[M+H]^+$: 203.1548, found 203.1543.



34

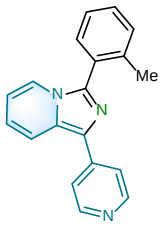
3-(dec-9-en-1-yl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), undec-10-enal (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **34** (20.3 mg, 0.075 mmol, isolated yield 75%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3357, 3182, 3079, 2924, 2854, 1659, 1632, 1465, 1424, 1372, 1243, 995, 909, 789, 746, 721, 699, 633, 554, 523, 474. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.53 – 6.48 (m, 1H), 6.45 – 6.41 (m, 1H), 5.86 – 5.75 (m, 1H), 5.02 – 4.91 (m, 2H), 2.94 – 2.90 (m, 2H), 2.48 (s, 3H), 2.06 – 2.00 (m, 2H), 1.84 – 1.77 (m, 2H), 1.42 – 1.26 (m, 10H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.1, 137.3, 126.4, 126.3, 120.2, 118.1, 115.5, 114.1, 111.7, 33.7, 29.4, 29.3, 29.2, 29.0, 28.8, 27.2, 26.6, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{18}H_{26}N_2$ $[M+H]^+$: 271.2174, found 271.2171.



35

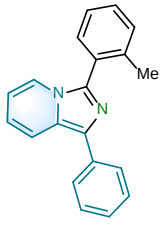
1-(pyridin-2-yl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridine-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **35** (21.4 mg, 0.075 mmol, isolated yield 75%) as a yellow solid. **Mp**: 90−92 ˚C. **FT-IR**: *v* (cm^{-1}): 2924, 2848, 1634, 1605, 1589, 1562, 1533, 1508, 1482, 1465, 1445, 1426, 1399, 1354, 1327, 1315, 1259, 1236, 1185, 1148, 1137, 1107, 1090, 1049, 1006, 942, 890, 868, 791, 777, 758, 744, 723, 711, 674, 624, 604, 542, 495, 443, 427, 404. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.66 – 8.61 (m, 1H), 8.58 – 8.55 (m, 1H), 8.18 – 8.14 (m, 1H), 7.65 – 7.61 (m, 1H), 7.59 – 7.55 (m, 1H), 7.46 – 7.43 (m, 1H), 7.37 – 7.25 (m, 3H), 7.05 – 6.99 (m, 1H), 6.89 – 6.83 (m, 1H), 6.57 – 6.51 (m, 1H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$):

δ 155.2, 149.0, 138.6, 137.7, 136.2, 130.8, 130.6, 129.9, 129.7, 129.2, 129.2, 126.1, 121.7, 121.6, 120.9, 120.3, 119.8, 113.6, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$: 286.1344, found 286.1341.



36

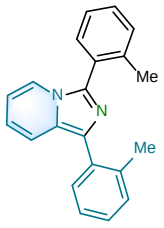
1-(pyridin-4-yl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of pyridin-2-yl(pyridin-4-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **36** (16.0 mg, 0.056 mmol, isolated yield 56%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2957, 2924, 2850, 1735, 1673, 1622, 1595, 1537, 1498, 1463, 1407, 1379, 1304, 1278, 1197, 1148, 1100, 987, 942, 824, 773, 723, 649, 616, 515, 451, 420. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.56 – 8.55 (m, 2H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.31 – 7.29 (m, 1H), 6.92 (dd, *J* = 9.3, 6.4 Hz, 1H), 6.60 – 6.56 (m, 1H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.3, 143.1, 139.0, 138.5, 131.0, 130.5, 130.0, 128.6, 127.6, 126.3, 122.7, 121.9, 121.0, 120.3, 118.5, 113.4, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$: 286.1344, found 286.1340.



37

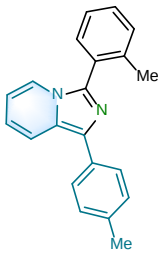
1-phenyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of phenyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **37** (21.9 mg, 0.077 mmol, isolated yield 77%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3048,

2927, 2851, 1663, 1628, 1599, 1508, 1490, 1447, 1354, 1315, 1242, 1179, 1142, 1102, 1074, 1004, 981, 946, 909, 771, 736, 694, 664, 616, 602, 499, 447, 418. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 – 7.87 (m, 2H), 7.80 – 7.77 (m, 1H), 7.54 – 7.51 (m, 1H), 7.43 – 7.36 (m, 3H), 7.34 – 7.28 (m, 2H), 7.27 – 7.17 (m, 2H), 6.72 – 6.68 (m, 1H), 6.45 – 6.41 (m, 1H), 2.18 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 137.8, 135.1, 131.1, 130.8, 130.6, 129.5, 129.2, 128.7, 126.6, 126.6, 126.3, 126.1, 121.9, 119.5, 118.9, 112.8, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{16}N_2$ $[M+H]^+$: 285.1392, found 285.1390.



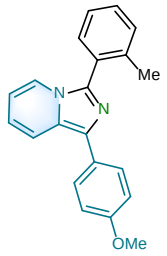
38

1,3-di-o-tolylimidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of pyridin-2-yl(*o*-tolyl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **38** (16.7 mg, 0.056 mmol, isolated yield 56%) as a green solid. **Mp**: 112−114 ˚C. **FT-IR**: *v* (cm^{-1}): 3056, 2918, 2854, 1663, 1601, 1517, 1482, 1455, 1354, 1306, 1257, 1133, 1102, 1039, 1010, 950, 793, 769, 758, 723, 703, 659, 616, 542, 453, 422. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.0 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.34 – 7.32 (m, 2H), 7.28 – 7.26 (m, 2H), 7.22 – 7.20 (m, 2H), 6.74 – 6.69 (m, 1H), 6.50 – 6.50 (m, 1H), 2.42 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 137.3, 130.9, 130.8, 130.3, 130.2, 129.4, 127.4, 127.4, 126.0, 125.5, 121.5, 118.9, 112.9, 20.7, 19.9. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2$ $[M+H]^+$: 299.1548, found 299.1545.



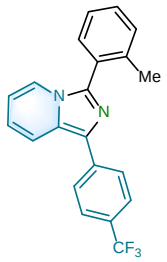
39

3-(o-tolyl)-1-(p-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of pyridin-2-yl(*p*-tolyl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **39** (21.8 mg, 0.073 mmol, isolated yield 73%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3031, 2926, 2856, 1909, 1661, 1607, 1539, 1508, 1409, 1358, 1311, 1259, 1245, 1179, 1107, 1039, 1001, 946, 818, 771, 746, 715, 645, 600, 571, 507, 451, 424. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 – 7.75 (m, 3H), 7.54 – 7.51 (m, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.27 – 7.23 (m, 1H), 7.21 – 7.18 (m, 2H), 6.71 – 6.67 (m, 1H), 6.45 – 6.41 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 137.6, 136.0, 132.3, 131.3, 130.8, 130.6, 129.5, 129.4, 129.3, 126.5, 126.3, 126.1, 121.8, 119.2, 119.1, 112.7, 21.2, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2$ $[M+H]^+$: 299.1548, found 299.1543.



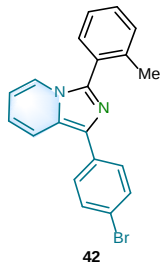
40

1-(4-methoxyphenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of (4-methoxyphenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **40** (22.0 mg, 0.070 mmol, isolated yield 70%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3066, 2930, 2848, 1657, 1599, 1539, 1500, 1459, 1412, 1356, 1298, 1284, 1245, 1179, 1102, 1028, 999, 942, 835, 771, 750, 725, 703, 647, 600, 577, 521, 449, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 9.3 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.24 (m, 1H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.68 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.45 – 6.41 (m, 1H), 3.79 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.4, 138.5, 137.5, 131.1, 130.8, 130.6, 129.5, 129.4, 127.9, 127.8, 126.1, 126.0, 121.8, 119.0, 118.9, 114.2, 112.7, 55.3, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2O$ $[M+H]^+$: 315.1497, found 315.1495.



41

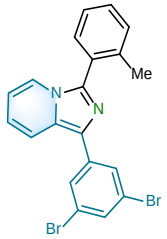
3-(o-tolyl)-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **41** (30.6 mg, 0.087 mmol, isolated yield 87%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3066, 2963, 2918, 2848, 1922, 1677, 1616, 1545, 1508, 1469, 1407, 1319, 1253, 1160, 1107, 1061, 1010, 981, 948, 847, 802, 771, 760, 729, 715, 703, 674, 618, 604, 544, 509, 455, 443, 424, 410. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 9.3 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.26 (m, 3H), 6.84 – 6.80 (m, 1H), 6.52 (t, *J* = 6.8 Hz, 1H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.7, 138.5, 138.4, 131.2, 130.9, 130.6, 129.8, 129.4, 128.9, 127.8 (q, $^2J_{C\text{-}F}$ = 32.1 Hz), 127.5, 126.3, 126.2, 125.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.5 (q, $^1J_{C\text{-}F}$ = 269.8 Hz), 122.3, 120.7, 118.6, 113.1, 19.8. **^{19}F NMR** (375 MHz, $CDCl_3$): δ -62.20. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{15}F_3N_2$ $[M+H]^+$: 353.1266, found 353.1263.



42

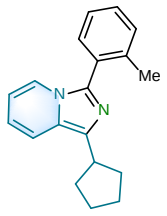
1-(4-bromophenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of (4-bromophenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **42** (30.0 mg, 0.083 mmol, isolated yield 83%) as a yellow solid. **Mp**: 123−125 ˚C. **FT-IR**: *v* (cm^{-1}): 2918, 2854, 2122, 1653, 1583, 1521, 1484, 1457, 1395, 1377, 1346, 1311, 1261, 1241, 1160, 1133, 1098, 1067, 1047, 1006, 981, 946, 828, 800, 771, 756, 723, 711, 699,

678, 633, 610, 598, 583, 505, 455, 437, 422. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 – 7.72 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.26 (m, 3H), 6.76 (dd, *J* = 9.2, 6.3 Hz, 1H), 6.50 – 6.46 (m, 1H), 2.18 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.5, 138.0, 134.1, 131.7, 130.9, 130.6, 129.9, 129.7, 129.0, 128.0, 126.8, 126.1, 122.1, 120.1, 120.0, 118.7, 112.9, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{15}BrN_2$ $[M+H]^+$: 363.0497, found 363.0493.



43

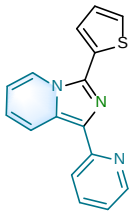
1-(3,5-dibromophenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of (3,5-dibromophenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **43** (27.7 mg, 0.063 mmol, isolated yield 63%) as a yellow solid. **Mp**: 139−140 ˚C. **FT-IR**: *v* (cm^{-1}): 3052, 2951, 2916, 2958, 1663, 1583, 1545, 1508, 1459, 1432, 1409, 1383, 1341, 1315, 1276, 1247, 1148, 1100, 1051, 1014, 983, 948, 861, 839, 806, 777, 738, 721, 705, 670, 620, 536, 451, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.47 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.26 (m, 3H), 6.87 – 6.83 (m, 1H), 6.55 – 6.51 (m, 1H), 2.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.7, 138.5, 138.4, 131.3, 130.9, 130.6, 129.9, 128.7, 127.9, 127.7, 127.4, 126.2, 123.2, 122.3, 121.1, 118.4, 113.2, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{14}Br_2N_2$ $[M+H]^+$: 440.9602, found 440.9609.



44

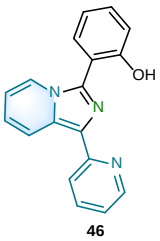
1-cyclopentyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of cyclopentyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (4 equiv.) and D-

glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **44** (22.6 mg, 0.082 mmol, isolated yield 82%) as a brown solid. **Mp**: 72−74 ˚C. **FT-IR**: *v* (cm^{-1}): 3060, 2951, 2862, 1653, 1628, 1603, 1453, 1416, 1364, 1304, 1238, 1105, 1045, 995, 946, 771, 746, 723, 620, 453, 418. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 6.8 Hz, 1H), 7.36 (d, *J* = 9.2 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.18 (t, *J* = 6.7 Hz, 1H), 6.48 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.33 – 6.29 (m, 1H), 3.36 – 3.28 (m, 1H), 2.11 (s, 3H), 2.04 – 1.98 (m, 2H), 1.91 – 1.86 (m, 2H), 1.82 – 1.76 (m, 2H), 1.65 – 1.59 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4, 136.1, 135.9, 130.7, 130.4, 129.6, 129.1, 125.9, 125.8, 121.2, 118.2, 116.5, 112.2, 38.3, 33.4, 25.7, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{20}N_2$ $[M+H]^+$: 277.1705, found 277.1702.



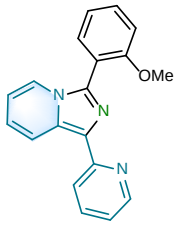
45

1-(pyridin-2-yl)-3-(thiophen-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), thiophene-2-carbaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **45** (16.1 mg, 0.058 mmol, isolated yield 58%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 9.2 Hz, 1H), 8.55 (d, *J* = 4.0 Hz, 1H), 8.30 – 8.28 (m, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.51 (d, *J* = 3.6 Hz, 1H), 7.39 (d, *J* = 5.2, 1H), 7.16 – 7.13 (m, 1H), 7.05 – 7.02 (m, 1H), 6.90 – 6.86 (m, 1H), 6.74 – 6.67 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 149.0, 136.3, 132.6, 132.1, 130.8, 130.4, 127.7, 126.4, 125.5, 122.0, 121.9, 121.1, 120.7, 120.1, 114.5. The compound is known, and the NMR data is in accordance with the previous literature.[234]



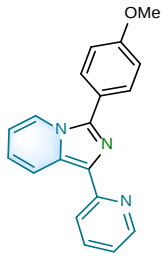
46

2-(1-(pyridin-2-yl)imidazo[1,5-a]pyridin-3-yl)phenol: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-hydroxybenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **46** (15.8 mg, 0.055 mmol, isolated yield 55%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 9.2 Hz, 1H), 8.57 – 8.55 (m, 1H), 8.47 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.67 (td, *J* = 8.0, 2.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.11 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.07 – 7.04 (m, 1H), 6.97 – 6.89 (m, 2H), 6.71 – 6.67 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.3, 153.8, 149.1, 136.4, 135.5, 130.1, 129.6, 128.6, 124.5, 122.3, 122.2, 121.7, 120.9, 119.8, 119.1, 117.8, 114.8, 114.0. The compound is known, and the NMR data is in accordance with the previous literature.[330]



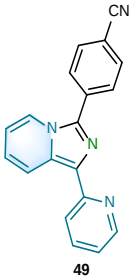
47

3-(2-methoxyphenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-methoxylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **47** (19.3 mg, 0.064 mmol, isolated yield 64%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.63 – 8.61 (m, 1H), 8.56 – 8.54 (m, 1H), 8.18 – 8.15 (m, 1H), 7.64 – 7.58 (m, 2H), 7.55 – 7.53 (m, 1H), 7.44 – 7.39 (m, 1H), 7.09 – 7.04 (m, 1H), 7.01 – 6.97 (m, 2H), 6.88 – 6.84 (m, 1H), 6.55 – 6.51 (m, 1H), 3.73 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.6, 155.3, 148.9, 136.2, 136.1, 132.8, 131.0, 130.2, 130.0, 123.3, 121.3, 121.2, 120.9, 120.2, 119.8, 119.1, 112.7, 111.2, 55.6. The compound is known, and the NMR data is in accordance with the previous literature.[226]



48

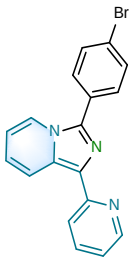
3-(4-methoxyphenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-methoxylbenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **48** (21.2 mg, 0.067 mmol, isolated yield 67%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 9.2 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.65 – 7.61 (m, 1H), 7.02 – 6.98 (m, 3H), 6.82 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.56 – 6.53 (m, 1H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.1, 155.1, 148.9, 138.1, 136.2, 130.2, 129.9, 129.9, 122.5, 121.7, 121.6, 120.8, 120.3, 119.9, 114.5, 113.7, 55.4. The compound is known, and the NMR data is in accordance with the previous literature.[330]



49

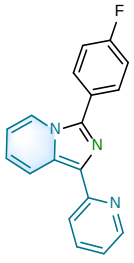
4-(1-(pyridin-2-yl)imidazo[1,5-a]pyridin-3-yl)benzonitrile: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-formylbenzonitrile (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **49** (24.0 mg, 0.081 mmol, isolated yield 81 %) as a yellow solid. **Mp**: 140−142 ˚C. **FT-IR**: *v* (cm^{-1}): 3384, 3309, 3200, 3058, 2928, 2850, 2230, 2217, 1667, 1603, 1591, 1564, 1513, 1484, 1457, 1434, 1409, 1352, 1311, 1278, 1255, 1170, 1148, 1105, 1084, 1061, 1008, 993, 946, 845, 816, 779, 748, 734, 721, 694, 661, 628, 616, 585, 558, 544, 525, 486, 433. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 9.2 Hz, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.75 (d, *J* = 7.6, 2H), 7.69 – 7.65 (m, 1H), 7.08 – 7.05 (m, 1H), 6.96 – 6.91 (m, 1H), 6.71 – 6.68 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 149.0, 136.4, 135.7, 134.5, 132.8, 131.9,

131.8, 131.1, 130.1, 128.2, 122.2, 121.8, 121.3, 120.9, 120.0, 118.6, 115.0, 111.8. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{12}N_4$ $[M+H]^+$: 297.1140, found 297.1136.



50

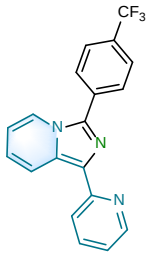
3-(4-bromophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-bromobenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. work-up gave product **50** (26.5 mg, 0.076 mmol, isolated yield 76%) as a brown solid. **FT-IR**: *v* (cm^{-1}): 2920, 2852, 2125, 1733, 1667, 1589, 1508, 1477, 1397, 1313, 1247, 1140, 1121, 1067, 1006, 950, 830, 785, 736, 696, 626, 593, 542, 488, 431, 406. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 9.2 Hz, 1H), 8.56 – 8.55 (m, 1H), 8.16 – 8.13 (m, 2H), 7.68 – 7.60 (m, 5H), 7.05 – 7.02 (m, 1H), 6.89 – 6.85 (m, 1H), 6.61 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 149.0, 136.8, 136.3, 132.3, 130.9, 130.4, 129.7, 129.1, 122.9, 122.0, 121.3, 121.2, 120.6, 119.9, 114.3. The compound is known, and the NMR data is in accordance with the previous literature.[331]



51

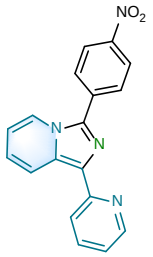
3-(4-fluorophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-fluorobenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **51** (23.1 mg, 0.080 mmol, isolated yield 80%) as a yellow solid. **Mp**: 116−117 ˚C. **FT-IR**: *v* (cm^{-1}): 2930, 2112, 1630, 1591, 1562, 1527, 1513, 1480, 1405, 1350, 1311, 1280,

1251, 1216, 1193, 1154, 1088, 1010, 948, 837, 810, 787, 734, 713, 690, 657, 628, 587, 565, 513, 433, 406. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 9.2 Hz, 1H), 8.56 – 8.54 (m, 1H), 8.14 (d, *J* = 8.0, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.75 – 7.72 (m, 2H), 7.65 – 7.61 (m, 1H), 7.18 – 7.14 (m, 2H), 7.03 – 7.00 (m, 1H), 6.86 – 6.82 (m, 1H), 6.59 – 6.55 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.0 (d, $^{1}J_{C\text{-}F}$ = 249.4 Hz), 154.9, 149.0, 137.0, 136.2, 130.6, 130.3 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 130.1, 126.3 (d, $^{4}J_{C\text{-}F}$ = 3.4 Hz), 121.9, 121.3, 121.0, 120.5, 119.8, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 114.1. **^{19}F NMR** (375 MHz, $CDCl_3$): δ -111.55. **ESI-HRMS**: *m/z* calcd. for $C_{18}H_{12}FN_3$ $[M+H]^+$: 290.1094, found 290.1090.



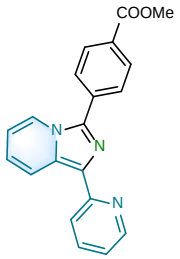
52

1-(pyridin-2-yl)-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-(trifluoromethyl)benzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **52** (28.1 mg, 0.083 mmol, isolated yield 83%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.69 – 8.66 (m, 1H), 8.57 – 8.55 (m, 1H), 8.12 – 8.15 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.68 – 7.63 (m, 1H), 7.06 – 7.02 (m, 1H), 6.91 – 6.87 (m, 1H), 6.66 – 6.62 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.7, 149.0, 136.3, 136.3, 133.6 (q, $^{4}J_{C\text{-}F}$ = 1.5 Hz), 131.3, 130.7, 130.5 (q, $^{2}J_{C\text{-}F}$ = 32.7 Hz), 128.3, 126.0 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 124.0 (q, $^{1}J_{C\text{-}F}$ = 272.1 Hz), 122.1, 121.4, 121.3, 120.7, 120.0, 114.6. **^{19}F NMR** (375 MHz, $CDCl_3$): δ -62.66. The compound is known, and the NMR data is in accordance with the previous literature.[332]



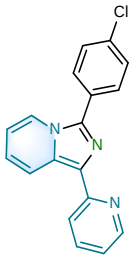
53

3-(4-nitrophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-nitrobenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **53** (25.6 mg, 0.081 mmol, isolated yield 81%) as a red solid. **Mp**: 225−226 ˚C. **FT-IR**: *v* (cm^{-1}): 2916, 1683, 1589, 1566, 1519, 1504, 1480, 1449, 1412, 1346, 1321, 1306, 1249, 1175, 1100, 1084, 1014, 950, 851, 785, 729, 694, 628, 591, 525, 478, 424. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.75 (dt, *J* = 9.2, 1.2 Hz, 1H), 8.59 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 8.36 – 8.23 (m, 3H), 8.21 – 8.18 (m, 1H). 8.06 – 8.01 (m, 2H), 7.73 – 7.67 (m, 1H), 7.09 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 6.98 (ddd, *J* = 9.2, 6.5, 0.9 Hz, 1H), 6.74 (ddd, *J* = 7.1, 6.4, 1.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.9, 147.2, 136.6, 136.3, 136.3, 135.8, 135.5, 131.4, 128.2, 124.4, 122.3, 122.1, 121.4, 121.1, 120.2, 115.3. **ESI-HRMS**: m/z calcd. for $C_{18}H_{12}N_4O_2$ $[M+H]^+$: 317.1039, found 317.1036.



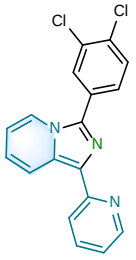
54

methyl 4-(1-(pyridin-2-yl)imidazo[1,5-a]pyridin-3-yl)benzoate: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), methyl-4-formylbenzoate (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **54** (13.5 mg, 0.041 mmol, isolated yield 41%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2918, 1719, 1681, 1581, 1523, 1467, 1430, 1317, 1278, 1189, 1105, 1018, 993, 946, 868, 824, 777, 746, 696, 664, 614, 534, 439. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.70 (d, *J* = 9.3 Hz, 1H), 8.58 (ddd, *J* = 5.1, 1.5, 0.9 Hz, 1H), 8.28 – 8.25 (m, 1H), 8.21 – 8.18 (m, 1H), 8.17 – 8.13 (m, 2H), 7.93 – 7.89 (m, 2H), 7.71 – 7.65 (m, 1H), 7.07 (ddd, *J* = 7.2, 5.1, 1.2 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.70 – 6.65 (m, 1H), 3.91 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.6, 149.7, 149.2, 137.0, 136.8, 130.3, 129.8, 129.0, 127.9, 126.4, 125.3, 123.5, 122.0, 121.6, 121.3, 120.8, 52.3. **ESI-HRMS**: m/z calcd. for $C_{18}H_{15}N_3O_2$ $[M+H]^+$: 330.1243, found 330.1236.



55

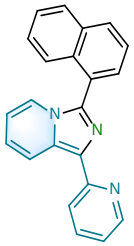
3-(4-chlorophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 4-chlorobenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **55** (25.0 mg, 0.082 mmol, isolated yield 82%) as a yellow solid. **Mp**: 137−138 ˚C. **FT-IR**: *v* (cm^{-1}): 2922, 2854, 2100, 1673, 1587, 1560, 1502, 1480, 1403, 1313, 1245, 1197, 1173, 1146, 1123, 1086, 1010, 952, 833, 781, 740, 713, 699, 628, 608, 596, 581, 492, 429, 406. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 10.4 Hz, 1H), 8.56 (s, 1H), 8.17 – 8.14 (m, 2H), 7.74 – 7.71 (m, 2H), 7.67 – 7.64 (m, 1H), 7.47 – 7.44 (m, 2H), 7.05 – 7.03 (m, 1H), 6.89 – 6.86 (m, 1H), 6.63 – 6.60 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.9, 149.0, 136.8, 136.3, 134.8, 130.9, 130.4, 129.5, 129.3, 128.6, 122.0, 121.4, 121.1, 120.6, 119.9, 114.2. **ESI-HRMS**: m/z calcd. for $C_{18}H_{12}ClN_3$ $[M+H]^+$: 306.0798, found 306.0795.



56

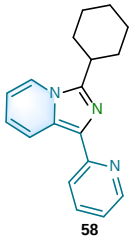
3-(3,4-dichlorophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 3,4-dichlorobenzaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **56** (24.4 mg, 0.072 mmol, isolated yield 72%) as a yellow solid. **Mp**: 177−179 ˚C. **FT-IR**: *v* (cm^{-1}): 2922, 2850, 2112, 1669, 1632, 1591, 1566, 1531, 1506, 1477, 1453, 1401, 1381, 1352, 1313, 1247, 1133, 1088, 1030, 1012, 954, 878, 828, 812, 783, 727, 703, 672, 628, 600, 532, 507, 455, 435, 412. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 9.2 Hz, 1H), 8.56 (d, *J* = 4.0 Hz, 1H), 8.16 (d, *J* = 7.2 Hz, 2H), 7.92 (s, 1H), 7.68 – 7.63 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.07 – 7.04 (m, 1H),

6.92 – 6.88 (m, 1H), 6.68 – 6.65 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.7, 149.0, 136.3, 135.5, 133.4, 132.8, 131.2, 131.0, 130.6, 130.1, 130.0, 127.1, 122.1, 121.4, 121.2, 120.8, 120.0, 114.6. **ESI-HRMS**: m/z calcd. for $C_{18}H_{11}Cl_2N_3$ $[M+H]^+$: 340.0408, found 340.0404.



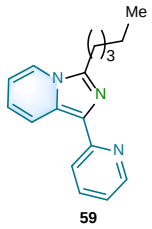
57

3-(naphthalen-1-yl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 1-naphthaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **57** (18.6 mg, 0.058 mmol, isolated yield 58%) as a yellow solid. **Mp**: 71−73 ˚C. **FT-IR**: *v* (cm^{-1}): 3050, 2924, 2850, 1663, 1585, 1529, 1508, 1473, 1426, 1401, 1352, 1304, 1245, 1214, 1142, 1076, 999, 969, 938, 802, 775, 740, 729, 705, 670, 616, 596, 530, 511, 418. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 8.8 Hz, 1H), 8.60 (d, *J* = 4.0 Hz, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.68 – 7.55 (m, 4H), 7.50 – 7.38 (m, 2H), 7.06 – 7.03 (m, 1H), 6.91 – 6.87 (m, 1H), 6.51 – 6.48 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.2, 149.0, 136.8, 136.3, 134.0, 132.0, 130.4, 130.1, 129.8, 129.0, 128.6, 127.1, 126.4, 125.5, 125.4, 122.0, 121.7, 121.2, 120.4, 120.0, 113.6. **ESI-HRMS**: m/z calcd. for $C_{22}H_{15}N_3$ $[M+H]^+$: 322.1344, found 322.1342.



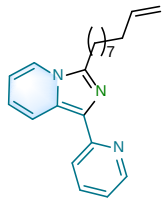
58

3-cyclohexyl-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), cyclohexanecarbaldehyde (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **58** (20.8 mg, 0.075 mmol, isolated yield 75%) as a yellow solid. **Mp**: 107−109 ˚C. **FT-IR**: *v* (cm^{-1}): 2926, 2852, 1632, 1587, 1562, 1533, 1519, 1471, 1445, 1428, 1401, 1346, 1284, 1224, 1146, 1086, 1059, 1001, 958, 890, 822, 791, 736, 703, 633, 616, 598, 509, 424, 408. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.62 – 8.58 (m, 2H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.07 – 7.04 (m, 1H), 6.84 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.62 – 6.58 (m, 1H), 3.01 (tt, *J* = 11.3, 3.0 Hz, 1H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.98 – 1.83 (m, 5H), 1.53 – 1.40 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.3, 148.9, 142.8, 136.0, 128.9, 128.7, 121.6, 120.7, 119.9, 119.9, 119.7, 112.7, 35.8, 30.6, 26.2, 25.9. **ESI-HRMS**: m/z calcd. for $C_{18}H_{19}N_3$ $[M+H]^+$: 278.1657, found 278.1654.



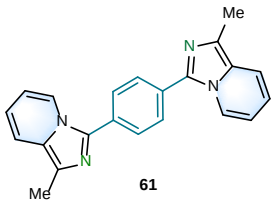
59

3-pentyl-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), hexanal (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **59** (20.4 mg, 0.077 mmol, isolated yield 77%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3037, 2936, 2858, 1686, 1681, 1630, 1587, 1533, 1519, 1463, 1428, 1405, 1374, 1341, 1323, 1286, 1241, 1220, 1179, 1148, 1115, 1088, 1065, 1028, 1004, 954, 886, 830, 787, 762, 734, 723, 699, 674, 631, 614, 579, 418, 404. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.52 – 8.48 (m, 2H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.60 (td, *J* = 7.6, 1.6 Hz, 1H), 6.96 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 6.76 (ddd, *J* = 9.2, 6.4, 0.8 Hz, 1H), 6.55 – 6.51(m, 1H), 2.93 (t, *J* = 8.0 Hz, 2H), 1.78 (p, *J* = 8.0 Hz, 2H), 1.38 – 1.28 (m, 4H), 0.84 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.1, 148.9, 139.1, 136.1, 129.0, 128.7, 121.6, 120.8, 120.0, 120.0, 119.6, 113.1, 31.6, 26.8, 26.7, 22.4, 14.0. **ESI-HRMS**: m/z calcd. for $C_{17}H_{19}N_3$ $[M+H]^+$: 266.1657, found 266.1654.



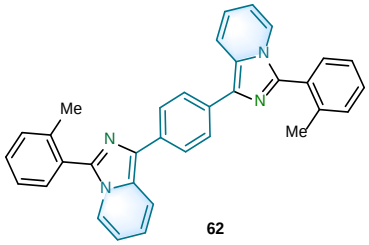
60

3-(dec-9-en-1-yl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure B**2, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), undec-10-enal (4 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **60** (23.3 mg, 0.070 mmol, isolated yield 70%) as a dark liquid. **FT-IR**: *v* (cm^{-1}): 3338, 3079, 2926, 2856, 1679, 1640, 1587, 1537, 1521, 1473, 1428, 1403, 1381, 1321, 1276, 1238, 1144, 1086, 1049, 995, 960, 909, 787, 738, 725, 678, 631, 612, 420, 402. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.61 – 8.57 (m, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.07 – 7.03 (m, 1H), 6.86 – 6.82 (m, 1H), 6.63 – 6.59 (m, 1H), 5.87 – 5.77 (m, 1H), 5.03 – 4.92 (m, 2H), 3.04 – 2.99 (m, 2H), 2.05 (q, *J* = 7.0 Hz, 2H), 1.87 (p, *J* = 7.7 Hz, 2H), 1.49 – 1.44 (m, 2H), 1.40 – 1.35 (m, 4H), 1.34 – 1.29 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.2, 148.9, 139.1, 139.0, 136.0, 129.0, 128.7, 121.5, 120.7, 119.9, 119.9, 119.5, 114.1, 113.0, 33.7, 29.4, 29.3, 29.2, 29.0, 28.8, 27.1, 26.7. **ESI-HRMS**: m/z calcd. for $C_{22}H_{27}N_3$ $[M+H]^+$: 334.2283, found 334.2280.



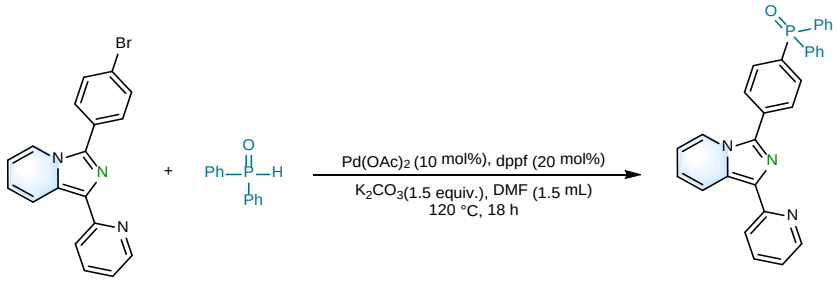
61

1,4-bis(1-methylimidazo[1,5-a]pyridin-3-yl)benzene: a mixture of 2-acetylpyridine (0.3 mmol), terephthaldehyde (0.1 mmol) and D-glucosamine·HCl (0.4 mmol) in AcOH : H_2O (1.8 : 0.2 mL) were stirred at 120 ˚C under Ar atmosphere for 3 days. Work-up gave product **61** (17.2 mg, 0.051 mmol, isolated yield 51%) as a brown red solid. **Mp**: 212−214 ˚C. **FT-IR**: *v* (cm^{-1}): 3070, 3035, 2920, 2858, 2110, 1927, 1663, 1630, 1537, 1510, 1442, 1424, 1407, 1356, 1327, 1306, 1253, 1179, 1115, 1078, 1008, 942, 837, 736, 678, 581, 548, 503, 422, 410. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 – 8.16 (m, 2H), 7.87 – 7.86 (m, 4H), 7.37 – 7.33 (m, 2H), 6.60 – 6.55 (m, 2H), 6.49 – 6.45 (m, 2H), 2.52 (s, 6H). **^{13}C NMR** (100 MHz, v): δ 136.0, 130.1, 129.3, 128.3, 128.0, 121.2, 118.4, 117.2, 113.2, 12.6. **ESI-HRMS**: m/z calcd. for $C_{22}H_{18}N_4$ $[M+H]^+$: 338.1531, found 338.1528.



62

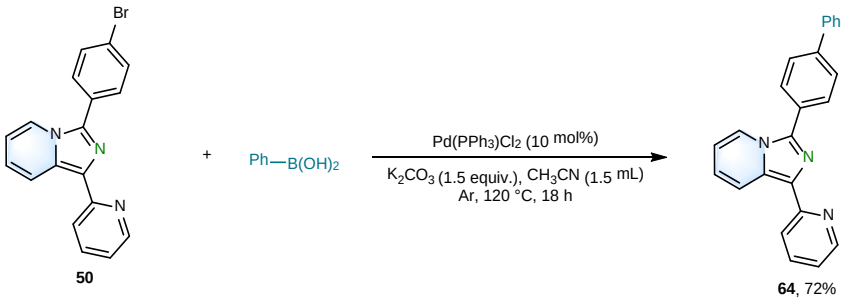
1,4-bis(3-(o-tolyl)imidazo[1,5-a]pyridin-1-yl)benzene: A mixture of 1,4-phenylenebis(pyridin-2-ylmethanone) (0.1 mmol), 2-methylbenzaldehyde (0.6 mmol) and D-glucosamine·HCl (0.4 mmol) in AcOH : H_2O (2.7 : 0.3 mL) were stirred at 120 ˚C under Ar atmosphere for 3 days. Work-up gave product **62** (17.6 mg, 0.036 mmol, isolated yield 36%) as a brown solid. **Mp**: 98−100 ˚C. **FT-IR**: *v* (cm^{-1}): 3058, 2920, 2852, 2110, 1869, 1745, 1661, 1599, 1510, 1455, 1428, 1377, 1356, 1306, 1276, 1241, 1158, 1105, 1043, 1004, 942, 843, 804, 773, 746, 727, 709, 616, 579, 519, 449, 424. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (s, 4H), 7.87 – 7.84 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.36 – 7.25 (m, 6H), 6.76 – 6.72 (m, 2H), 6.48 – 6.45 (m, 2H), 2.21 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.6, 137.8, 133.1, 131.2, 130.8, 130.7, 129.5, 129.3, 126.8, 126.7, 126.1, 121.9, 119.4, 119.2, 112.8, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{34}H_{26}N_4$ $[M+H]^+$: 491.2236, found 491.2240.



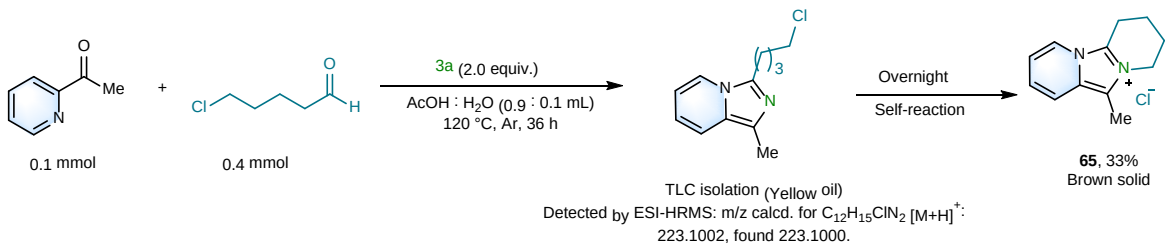
50 **63**, 68%

A mixture of 3-(4-bromophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine **50** (0.1 mmol), diphenylphosphine oxide (1.5 equiv.), $Pd(OAc)_2$ (10 mol%), dppf (20 mol%) and K_2CO_3 (1.5 equiv.) in the DMF (1.5 mL) were stirred at 120 ˚C under Ar atmosphere for 18 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by thermometer. After the reaction completely, the reaction solution was filtrated and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane : Et_3N) to give products **63** (32.0 mg, isolated yield 68%) as a yellow solid. **Mp**: 102−104 ˚C; **FT-IR**: *v* (cm^{-1}): 2918, 2623, 2498, 1679, 1589, 1510, 1477, 1434, 1395, 1311, 1251, 1175, 1109, 1010, 995, 948, 841, 791, 744, 719, 692, 643, 552, 538, 422. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 9.2 Hz, 1H),

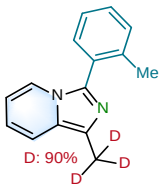
8.53 (d, *J* = 2.4 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.78 – 7.73 (m, 2H), 7.65 – 7.60 (m, 5H), 7.51 – 7.47 (m, 2H), 7.42 – 7.39 (m, 4H), 7.03 – 7.00 (m, 1H), 6.90 – 6.85 (m, 1H), 6.63 – 6.60 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.5, 149.1, 148.8, 136.6 (d, J_{C-P} = 15.6 Hz), 136.3, 133.5 (d, J_{C-P} = 2.9 Hz), 132.7 (d, J_{C-P} = 10.1 Hz), 132.1 (d, J_{C-P} = 2.7 Hz), 132.0 (d, J_{C-P} = 10.0 Hz), 131.1, 130.7, 128.5 (d, $^2J_{C-P}$ = 12.2 Hz), 127.8 (d, $^2J_{C-P}$ = 12.2 Hz), 125.8 (d, $^1J_{C-P}$ = 116.6 Hz), 121.9, 121.5, 121.4, 120.6, 119.9, 114.5. **^{31}P NMR** (162 MHz, $CDCl_3$): δ 29.0. **EI-HRMS (FTMS + p EI Full ms)**: m/z calcd. for $C_{30}H_{22}N_3OP$ [M]: 471.1500, found 471.1486.



A mixture of 3-(4-bromophenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine **50** (0.1 mmol), phenylboronic acid (1.5 equiv.), $Pd(PPh_3)Cl_2$ (10 mol%) and K_2CO_3 (1.5 equiv.) in the CH_3CN (1.5 mL) were stirred at 120 ˚C under Ar atmosphere for 18 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by thermometer. After reaction completely, the reaction mixture was filtrated and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane : Et_3N) to give products **64** (25.0 mg, isolated yield 72%) as a green solid. **Mp**: 160−162 ˚C; **FT-IR**: *v* (cm^{-1}): 2965, 2920, 2850, 2112, 1673, 1585, 1560, 1529, 1513, 1496, 1480, 1447, 1430, 1403, 1335, 1313, 1302, 125, 1193, 1140, 1086, 1008, 948, 853, 789, 760, 738, 723, 696, 664, 631, 596, 550, 517, 482, 435. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.68 (d, *J* = 9.0 Hz, 1H), 8.58 (d, *J* = 4.2 Hz, 1H), 8.24 (dd, *J* = 14.5, 7.6 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 6.9 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.89 (dd, *J* = 9.0, 6.6 Hz, 1H), 6.63 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 154.8, 148.8, 141.7, 140.4, 137.9, 136.5, 132.6, 130.4, 129.1, 128.9, 128.7, 127.7, 127.2, 127.1, 121.9, 121.7, 121.2, 120.5, 120.1, 114.1. **ESI-HRMS**: m/z calcd. for $C_{24}H_{17}N_3$ $[M+H]^+$: 348.1501, found 348.1498.



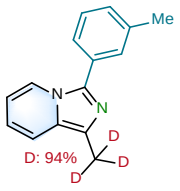
A mixture of 2-acetylpyridine (0.1 mmol), 5-chloropentanal (4.0 equiv.), D-glucosamine·HCl (2.0 equiv.) in the AcOH : H_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. 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 filtrated and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane : Et_3N) to give products 3-(4-chlorobutyl)-1-methylimidazo[1,5-a]pyridine as a yellow oil, which then transform to final product **65** in glass bottle through self-reaction under air atmosphere in room temperature overnight. Finally the crude product **65** was washed by *n*-hexane (2 mL) for 3 times and ethyl acetate (2 mL) for 3 times to obtain pure product **65** (25.0 mg, overall isolated yield 33%). **Mp**: 115−117 ˚C. **FT-IR**: *v* (cm^{-1}): 3436, 3379, 3031, 2953, 2926, 2858, 1723, 1653, 1611, 1533, 1434, 1358, 1255, 1041, 806, 744, 536. **^{1}H NMR** (300 MHz, CD_3OD): δ 8.20 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.18 – 7.06 (m, 2H), 4.39 (t, *J* = 5.7 Hz, 2H), 3.29 (t, *J* = 6.2 Hz, 2H), 2.65 (s, 3H), 2.31 – 2.17 (m, 4H). **^{13}C NMR** (100 MHz, CD_3OD): δ 134.7, 127.1, 123.5, 122.4, 121.6, 118.7, 118.0, 45.7, 22.6, 21.5, 19.0, 7.8. **ESI-HRMS**: m/z calcd. for $C_{12}H_{15}N_2$ [M]: 187.1230, found 187.1240.



66

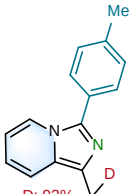
1-(methyl-d_3)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **66** (10.8 mg, 0.048 mmol, isolated yield 48%) as a yellow solid. **Mp**: 60−61 ˚C. **FT-IR**: *v* (cm^{-1}): 3050, 2918, 2852, 1669, 1517, 1453, 1412, 1362, 1247, 1100, 1044, 1016, 993, 958, 773, 727, 678, 649, 451, 422. D incorporation was tested by ^{1}H NMR: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.2

Hz, 1H), 7.36 – 7.22 (m, 5H), 6.53 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.37 – 6.33 (m, 1H), 2.47 (0.3H), 2.13 (s, 3H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2$ $[M+H]^+$: 226.1424, found 226.1420.



67

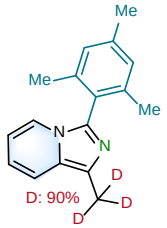
1-(methyl-d3)-3-(m-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **67** (13.3 mg, 0.059 mmol, isolated yield 59%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3050, 2918, 2854, 1671, 1605, 1583, 1517, 1465, 1362, 1255, 1203, 1090, 1028, 997, 971, 884, 791, 734, 696, 657, 618, 528, 439, 420. D incorporation was tested by ^{1}H NMR: 94%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 7.2 Hz, 1H), 7.54 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.54 (dd, *J* = 9.1, 6.3 Hz, 1H), 6.41 (t, *J* = 6.9 Hz, 1H), 2.47 (0.19H), 2.36 (s, 3H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2$ $[M+H]^+$: 226.1424, found 226.1420.



68

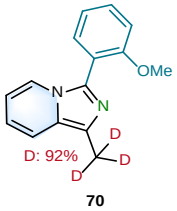
1-(methyl-d3)-3-(p-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **68** (15.1 mg, 0.067 mmol, isolated yield 67%) as a yellow solid. **Mp**: 49-50 ˚C. **FT-IR**: *v* (cm^{-1}): 3019, 2916, 2854, 1661, 1609, 1529, 1457, 1409, 1364, 1251, 1177, 1111, 1041, 1016, 958, 820, 725, 676, 637, 573, 490, 422. D incorporation was tested by ^{1}H NMR: 93%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.53 (dd, *J* =

9.1, 6.3 Hz, 1H), 6.42 – 6.37 (m, 1H), 2.46 (0.22H), 2.34 (s, 3H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2$ $[M+H]^+$: 226.1424, found 226.1419.



69

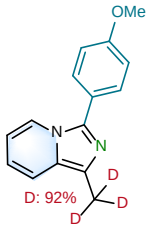
3-mesityl-1-(methyl-d3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2,4,6-trimethylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **69** (11.4 mg, 0.045 mmol, isolated yield 45%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2918, 2850, 1611, 1521, 1461, 1412, 1362, 1321, 1243, 1187, 1127, 1034, 1016, 993, 966, 940, 851, 773, 734, 682, 585, 420. D incorporation was tested by ^{1}H NMR: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 9.3 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.89 (s, 2H), 6.51 (dd, *J* = 9.1, 6.3 Hz, 1H), 6.33 – 6.29 (m, 1H), 2.48 (0.30H), 2.27 (s, 3H), 1.88 (s, 6H). **ESI-HRMS**: m/z calcd. for $C_{17}H_{15}D_3N_2$ $[M+H]^+$: 254.1737, found 254.1733.



70

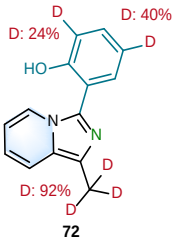
3-(2-methoxyphenyl)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-methoxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **70** (14.7 mg, 0.061 mmol, isolated yield 61%) as a yellow solid. **Mp**: 66−68 ˚C. **FT-IR**: *v* (cm^{-1}): 2926, 2838, 1657, 1632, 1601, 1578, 1519, 1463, 1434, 1414, 1370, 1241, 1160, 1105, 1045, 1016,

960, 793, 750, 732, 678, 649, 573, 521, 492, 422. D incorporation was tested by ^{1}H NMR: 92%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.04 – 7.00 (m, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.39 – 6.34 (m, 1H), 3.73 (s, 3H), 2.48 (0.25H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2O$ $[M+H]^+$: 242.1373, found 242.1368.



71

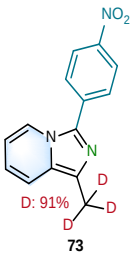
3-(4-methoxyphenyl)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-methoxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **71** (15.7 mg, 0.065 mmol, isolated yield 65%) as a yellow solid. **Mp**: 50−52 ˚C. **FT-IR**: *v* (cm^{-1}): 2998, 2932, 2835, 1665, 1607, 1570, 1527, 1461, 1438, 1407, 1366, 1300, 1288, 1247, 1170, 1111, 1020, 958, 833, 727, 676, 604, 575, 513, 416. D incorporation was tested by ^{1}H NMR: 92%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.52 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.41 – 6.37 (m, 1H), 3.80 (s, 3H), 2.46 (0.23H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2O$ $[M+H]^+$: 242.1373, found 242.1368.



72

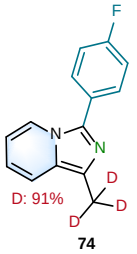
2-(1-(methyl-d_3)imidazo[1,5-a]pyridin-3-yl)phen-4,6-d_2-ol: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 2-hydroxylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up

gave product **72** (11.9 mg, 0.052 mmol, isolated yield 52%) as a white solid. **Mp**: 129−131 ˚C. **FT-IR**: *v* (cm^{-1}): 2924, 2850, 2120, 1741, 1634, 1607, 1578, 1519, 1436, 1416, 1372, 1292, 1259, 1234, 1179, 1096, 1041, 1018, 964, 913, 839, 808, 750, 727, 680, 641, 583, 544, 523, 420. D incorporation was tested by ^{1}H NMR: 92%, 40% and 24%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.37 (d, *J* = 7.3 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.19 (s, 1H), 7.07 (0.60H), 6.91 (0.76H), 6.63 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.57 – 6.52 (m, 1H), 2.45 (0.26H). **ESI-HRMS**: m/z calcd. for $C_{14}H_7D_5N_2O$ $[M+H]^+$: 230.1342, found 230.1330.



73

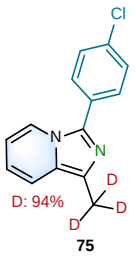
1-(methyl-d3)-3-(4-nitrophenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-nitrobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **73** (17.7 mg, 0.069 mmol, isolated yield 69%) as a red solid. **Mp**: 49−51 ˚C. **FT-IR**: *v* (cm^{-1}): 2951, 2918, 2850, 1681, 1591, 1510, 1422, 1344, 1309, 1255, 1175, 1098, 1078, 1016, 956, 913, 847, 750, 736, 719, 690, 666, 521, 490, 474, 420. D incorporation was tested by ^{1}H NMR: 91%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.30 – 8.27 (m, 2H), 8.23 (d, *J* = 7.2 Hz, 1H), 7.95 – 7.93 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.71 – 6.68 (m, 1H), 6.62 – 6.58 (m, 1H), 2.49 (0.27H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_3O_2$ $[M+H]^+$: 257.1118, found 257.1117.



74

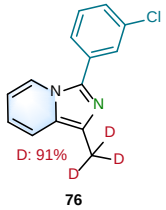
3-(4-fluorophenyl)-1-(methyl-d$_3$)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-fluorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up

gave product **74** (16.0 mg, 0.070 mmol, isolated yield 70%) as a yellow solid. **Mp**: 99-100 ˚C. **FT-IR**: *v* (cm^{-1}): 2955, 2921, 2852, 1659, 1603, 1525, 1506, 1461, 1414, 1377, 1222, 1156, 1096, 1014, 962, 839, 812, 765, 736, 673, 577, 517. D incorporation was tested by ^{1}H NMR: 91%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 6.9 Hz, 1H), 7.68 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.32 (d, *J* = 9.3 Hz, 1H), 7.12 (t, *J* = 8.7 Hz, 2H), 6.58 – 6.53 (m, 1H), 6.45 – 6.41 (m, 1H), 2.45 (0.26H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_2F$ $[M+H]^+$: 230.1173, found 230.1168.



75

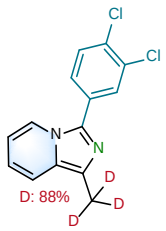
3-(4-chlorophenyl)-1-(methyl-d$_3$)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-chlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **75** (14.9 mg, 0.061 mmol, isolated yield 61%) as a yellow solid. **Mp**: 83−85 ˚C. **FT-IR**: *v* (cm^{-1}): 2951, 2914, 2844, 1659, 1591, 1506, 1480, 1403, 1374, 1253, 1173, 1088, 1012, 960, 833, 725, 670, 523, 484, 424. D incorporation was tested by ^{1}H NMR: 94%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.31 (m, 3H), 6.57 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.47 – 6.43 (m, 1H), 2.46 (0.18H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_2Cl$ $[M+H]^+$: 246.0877, found 246.0872.



76

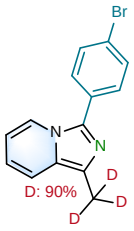
3-(3-chlorophenyl)-1-(methyl-d$_3$)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3-chlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0

equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **76** (15.4 mg, 0.063 mmol, isolated yield 63%) as a yellow solid. **Mp**: 89−90 ˚C. **FT-IR**: *v* (cm^{-1}): 2917, 1665, 1592, 1564, 1455, 1428, 1377, 1251, 1080, 995, 884, 787, 734, 688, 614, 414. D incorporation was tested by ^{1}H NMR: 91%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.72 (s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.28 (m, 3H), 6.61 – 6.56 (m, 1H), 6.49 – 6.45 (m, 1H), 2.46 (0.27H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3ClN_2$ $[M+H]^+$: 246.0877, found 246.0873.



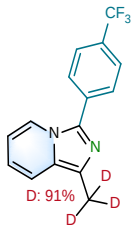
77

3-(3,4-dichlorophenyl)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 3,4-dichlorobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **77** (11.4 mg, 0.041 mmol, isolated yield 41%) as a yellow solid. **Mp**: 97−99 ˚C. **FT-IR**: *v* (cm^{-1}): 2916, 2852, 1671, 1589, 1554, 1496, 1451, 1416, 1397, 1249, 1131, 1028, 977, 874, 826, 729, 666, 573, 536, 519, 435, 420. D incorporation was tested by ^{1}H NMR: 88%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.5 Hz, 1H), 7.82 (s, 1H), 7.55 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.60 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.52 – 6.47 (m, 1H), 2.45 (0.37H). **ESI-HRMS**: m/z calcd. for $C_{14}H_7D_3Cl_2N_2$ $[M+H]^+$: 280.0488, found 280.0476.



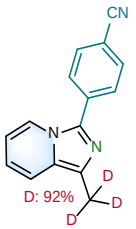
78

3-(4-bromophenyl)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-bromobenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **78** (19.4 mg, 0.067 mmol, isolated yield 67%) as a yellow solid. **Mp**: 86−88 ˚C. **FT-IR**: *v* (cm^{-1}): 2928, 2114, 1660, 1591, 1508, 1418, 1399, 1362, 1253, 1175, 1102, 1067, 1008, 958, 826, 723, 672, 490, 420. D incorporation was tested by ^{1}H NMR: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 6.6 Hz, 1H), 7.60 – 7.56 (m, 4H), 7.33 (d, *J* = 9.0 Hz, 1H), 6.59 – 6.54 (m, 1H), 6.47 – 6.42 (m, 1H), 2.45 (0.3H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_2Br$ $[M+H]^+$: 290.0372, found 290.0364.



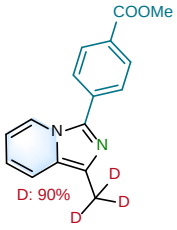
79

1-(methyl-d_3)-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-(trifluoromethyl)benzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **79** (22.9 mg, 0.082 mmol, isolated yield 82%) as a yellow solid. **Mp**: 73−74 ˚C. **FT-IR**: *v* (cm^{-1}): 2930, 1684, 1616, 1519, 1422, 1317, 1253, 1162, 1107, 1063, 1014, 958, 839, 732, 670, 602, 523, 497, 427. D incorporation was tested by ^{1}H NMR: 91%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.52 – 6.48 (m, 1H), 2.47 (0.28H). **ESI-HRMS**: m/z calcd. for $C_{15}H_8D_3F_3N_2$ $[M+H]^+$: 280.1141, found 280.1139.



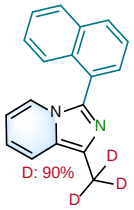
80

4-(1-(methyl-d$_3$)imidazo[1,5-a]pyridin-3-yl)benzonitrile: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 4-formylbenzonitrile (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **80** (16.5 mg, 0.070 mmol, isolated yield 70%) as a yellow solid. **Mp**: 117−118 ˚C. **FT-IR**: *v* (cm^{-1}): 3079, 2953, 2920, 2856, 2221, 2125, 1737, 1671, 1605, 1513, 1414, 1333, 1255, 1168, 1105, 1018, 956, 843, 727, 672, 593, 550, 533, 420. D incorporation was tested by ^{1}H NMR: 92%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 1H), 6.66 (dd, *J* = 9.0, 6.6 Hz, 1H), 6.55 (t, *J* = 6.6 Hz, 1H), 2.47 (0.23H). **ESI-HRMS**: m/z calcd. for $C_{15}H_8D_3N_3$ $[M+H]^+$: 237.1220, found 237.1219.



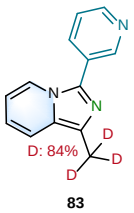
81

methyl 4-(1-(methyl-d3)imidazo[1,5-a]pyridin-3-yl)benzoate: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), methyl-4-formylbenzoate (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. work-up gave product **81** (10.5 mg, 0.039 mmol, isolated yield 39%) as a brown solid. **Mp**: 79−81 ˚C. **FT-IR**: *v* (cm^{-1}): 2916, 1714, 1609, 1436, 1278, 1175, 1102, 1014, 956, 859, 773, 701, 528, 486, 420. D incorporation was tested by ^{1}H NMR: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.53 – 6.48 (m, 1H), 3.88 (s, 3H), 2.47 (0.29H). **ESI-HRMS**: m/z calcd. for $C_{16}H_{11}D_3O_2N_2$ $[M+H]^+$: 270.1322, found 270.1316.



82

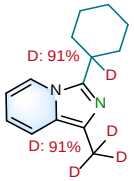
1-(methyl-d3)-3-(naphthalen-1-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), 1-naphthaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **82** (14.1 mg, 0.054 mmol, isolated yield 54%) as a yellow solid. **Mp**: 59−61 ˚C. **FT-IR**: *v* (cm^{-1}): 3056, 2918, 2850, 1646, 1587, 1508, 1442, 1409, 1364, 1327, 1247, 1210, 1144, 1004, 942, 864, 802, 773, 734, 680, 639, 573, 530, 495, 412. D incorporation was tested by ^{1}H NMR: 90%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 – 7.85 (m, 2H), 7.65 – 7.63 (m, 2H), 7.53 – 7.48 (m, 2H), 7.43 (d, *J* = 6.8 Hz, 1H), 7.39 – 7.36 (m, 2H), 6.59 – 6.55 (m, 1H), 6.34 – 6.30 (m, 1H), 2.53 (0.30H). **ESI-HRMS**: m/z calcd. for $C_{18}H_{11}D_3N_2$ $[M+H]^+$: 262.1424, found 262.1419.



83

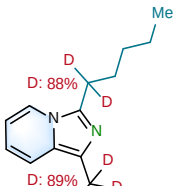
1-(methyl-d_3)-3-(pyridin-3-yl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), nicotinaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **83** (6.4 mg, 0.030 mmol, isolated yield 30%) as a yellow solid. **Mp**: 47−48 ˚C. **FT-IR**: *v* (cm^{-1}): 3037, 2926, 2854, 1677, 1630, 1568, 1517, 1422, 1366, 1327, 1255, 1181, 1154, 1022, 958, 810, 736, 705, 676, 616, 521, 420. D incorporation was tested by ^{1}H NMR: 84%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.00 (d, *J* = 1.2 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.15 – 8.12 (m, 2H), 7.44 – 7.39 (m, 2H), 6.69 (dd, *J* = 9.1,

6.4 Hz, 1H), 6.60 – 6.56 (t, *J* = 6.7 Hz, 1H), 2.52 (0.47H). **ESI-HRMS**: m/z calcd. for $C_{13}H_8D_3N_3$ $[M+H]^+$: 213.1220, found 213.1214.



84

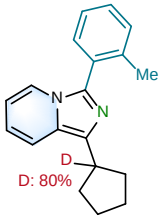
3-(cyclohexyl-1-d)-1-(methyl-d3)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), cyclohexanecarbaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **84** (15.7 mg, 0.072 mmol, isolated yield 72 %) as a yellow solid. **Mp**: 60−61 ˚C. **FT-IR**: *v* (cm^{-1}): 3342, 3173, 2928, 2854, 1626, 1445, 1405, 1245, 1142, 1090, 1022, 995, 960, 837, 816, 727, 696, 661, 587, 517, 499, 418. D incorporation was tested by ^{1}H NMR: 91% and 91%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 1H), 6.44 – 6.31 (m, 2H), δ 2.89 – 2.80 (0.09H). 2.38 (0.26H), 1.94 – 1.45 (m, 7H), 1.41 – 1.33 (m, 3H). **ESI-HRMS**: m/z calcd. for $C_{14}H_{14}D_4N_2$ $[M+H]^+$: 219.1799, found 219.1796.



85

1-(methyl-d3)-3-(pentyl-1,1-d2)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of 2-acetylpyridine (0.1 mmol), hexanal (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **85** (15.5 mg, 0.075 mmol, isolated yield 75%) as a brown solid. **Mp**: 106−107 ˚C. **FT-IR**: *v* (cm^{-1}): 3184, 2959, 2930, 2858, 1653, 1461, 1377, 1247, 1043, 995, 783, 734, 694, 618, 560, 418. D incorporation was tested by ^{1}H NMR: 89% and 88%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.2 Hz,

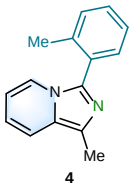
1H), 7.22 (d, *J* = 9.3 Hz, 1H), 6.44 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.38 – 6.34 (m, 1H), 2.83 (0.24H), 2.37 (0.33H), 1.72 (t, *J* = 6.3 Hz, 2H), 1.32 – 1.29 (m, 4H), 0.83 (t, *J* = 6.9 Hz, 3H). **ESI-HRMS**: m/z calcd. for $C_{13}H_{13}D_5N_2$ $[M+H]^+$: 208.1862, found 208.1858.



86

1-(cyclopentyl-1-d)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure B**1, a mixture of cyclopentyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzaldehyde (2 equiv.) and D-glucosamine·HCl (2.0 equiv.) in AcOH-d_4 : D_2O (0.9 : 0.1 mL) were stirred at 120 ˚C under Ar atmosphere for 36 h. Work-up gave product **86** (21.6 mg, 0.078 mmol, isolated yield 78%) as a brown liquid. **FT-IR**: *v* (cm^{-1}): 3064, 2951, 2866, 1688, 1632, 1517, 1453, 1412, 1362, 1306, 1243, 1222, 1137, 1105, 1043, 999, 944, 773, 746, 721, 616, 544, 453, 418. D incorporation was tested by ^{1}H NMR: 80%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.40 (m, 1H), 7.36 – 7.31 (m, 2H), 7.24 – 7.21 (m, 2H), 7.19 – 7.15 (m, 1H), 6.48 – 6.44 (m, 1H), 6.30 – 6.26 (m, 1H), 3.36 – 3.28 (0.2H), 2.11 (s, 3H), 2.03 – 1.98 (m, 2H), 1.92 – 1.85 (m, 2H), 1.81 – 1.77 (m, 2H), 1.64 – 1.59 (m, 2H). **ESI-HRMS**: m/z calcd. for $C_{19}H_{19}DN_2$ $[M+H]^+$: 278.1768, found 278.1759.

5.3.3 Direct nitrogen interception from chitin/chitosan for imidazo[1,5-a]pyridine

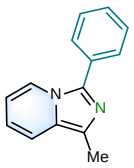


4

Methyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight.

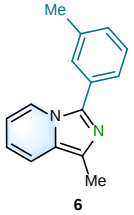
Work-up gave product **3** (16.9 mg, 0.076 mmol, isolated yield 76%) as a yellow liquid. Following the **General procedure C3**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (2.0 equiv.) and chitin (3.0 equiv.) in the CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC overnight. Work-up gave product **3** (15.8 mg, 0.071 mmol, isolated yield 71%) as a yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.35–7.17 (m, 5H), 6.53 – 6.48 (m, 1H), 6.35–6.30 (m, 1H), 2.49 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.1, 136.2, 130.6, 130.4, 129.5, 129.1, 127.9, 126.7, 125.9, 121.2, 118.0, 116.6, 112.2, 19.6, 12.6.



5

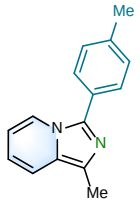
1-Methyl-3-phenylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), benzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **5** (17.1 mg, 0.082 mmol, isolated yield 82%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.30 (m, 2H), 6.56 – 6.52 (m, 1H), 6.43 – 6.39 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) 136.5, 130.3, 128.9, 128.4, 127.9, 127.7, 121.1, 118.3, 117.1, 112.9, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1230.



6

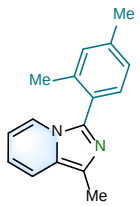
1-Methyl-3-(m-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 3-methylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight.

Work-up gave product **6** (17.8 mg, 0.080 mmol, isolated yield 80%) as a yellow solid. **m.p.**: 104-106 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.2 Hz, 1H), 7.53 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.54 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.42 – 6.39 (m, 1H), 2.48 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.8, 136.7, 132.7, 130.2, 129.2, 128.7, 128.6, 127.9, 124.5, 121.2, 118.3, 117.0, 112.8, 21.4, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1233.



7

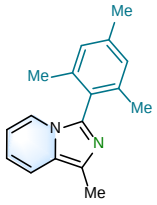
1-methyl-3-(p-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-methylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **7** (17.6 mg, 0.079 mmol, isolated yield 79%) as a yellow solid. **m.p.**: 62-63 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.52 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.41 – 6.37 (m, 1H), 2.49 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.4, 136.7, 129.6, 128.5, 127.7, 127.7, 127.4, 121.2, 118.3, 116.8, 112.7, 21.4, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{14}N_2$ $[M+H]^+$: 223.1235, found 223.1234.



8

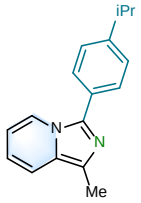
3-(2,4-dimethylphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2,4-dimethylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **8** (16.7 mg, 0.075 mmol, isolated yield 75%) as a brown solid. **m.p.**: 82-83 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.54 – 6.50 (m, 1H), 6.36 – 6.32 (m, 1H), 2.48 (s, 3H),

2.31 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.1, 137.9, 136.3, 131.4, 130.4, 127.6, 126.7, 126.4, 121.3, 118.0, 116.7, 112.2, 21.3, 19.5, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{16}N_2$ $[M+H]^+$: 237.1392, found 237.1389.



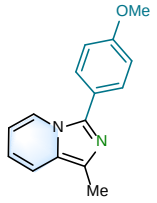
9

3-mesityl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2,4,6-trimethylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **9** (17.8 mg, 0.071 mmol, isolated yield 71%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.88 (s, 2H), 6.52 – 6.48 (m, 1H), 6.32 – 6.28 (m, 1H), 2.50 (s, 3H), 2.27 (s, 3H), 1.88 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.1, 135.5, 128.3, 127.5, 126.2, 126.2, 120.9, 118.0, 116.3, 112.1, 21.2, 19.5, 12.7. **ESI-HRMS**: m/z calcd. for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1548, found 251.1545.



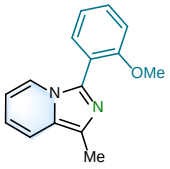
10

3-(4-isopropylphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-isopropylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **10** (18.5 mg, 0.074 mmol, isolated yield 74%) as a brown solid. **m.p.**: 61-63 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.26 (m, 3H), 6.53 (dd, *J* = 9.0, 6.4 Hz, 1H), 6.42 – 6.37 (m, 1H), 2.89 (hept, *J* = 6.9 Hz, 1H), 2.49 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.4, 136.5, 128.3, 127.8, 127.7, 127.4, 127.0, 121.2, 118.3, 117.0, 112.9, 34.0, 23.8, 12.3. **ESI-HRMS**: m/z calcd. for $C_{17}H_{18}N_2$ $[M+H]^+$: 251.1548, found 251.1544.



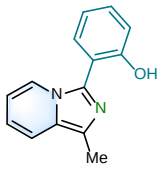
11

3-(4-methoxyphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-methoxylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **11** (15.5 mg, 0.065 mmol, isolated yield 65%) as a yellow solid. **m.p.**: 55−57 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 9.2 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.51 (dd, *J* = 9.2, 6.0 Hz, 1H), 6.40 – 6.37 (m, 1H), 3.79 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 136.5, 129.2, 128.3, 127.5, 122.8, 121.1, 118.3, 116.7, 114.4, 112.7, 55.3, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_4N_2O$ $[M+H]^+$: 239.0402, found 239.0397.



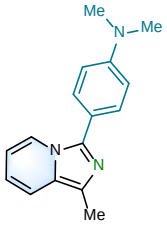
12

3-(2-methoxyphenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methoxylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **12** (14.99 mg, 0.063 mmol, isolated yield 63%) as a yellow solid. **m.p.**: 62−63 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.36 – 7.28 (m, 2H), 7.01 – 6.97 (m, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.54 – 6.50 (m, 1H), 6.36 – 6.32 (m, 1H), 3.70 (s, 3H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.1, 134.3, 132.3, 130.3, 128.1, 127.5, 122.8, 120.9, 119.2, 117.6, 116.7, 111.5, 111.0, 55.4, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{14}N_2O$ $[M+H]^+$: 239.1184, found 239.1181.



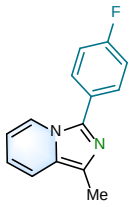
13

2-(1-methylimidazo[1,5-a]pyridin-3-yl)phenol: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2-hydoxylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **13** (6.7 mg, 0.030 mmol, isolated yield 30%) as a white solid. **m.p.**: 136−138 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 9.2 Hz, 1H), 7.19 – 7.18 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.92 – 6.88 (m, 1H), 6.64 – 6.60 (m, 1H), 6.55 – 6.51 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 134.2, 129.4, 127.2, 127.0, 123.9, 121.9, 118.9, 118.6, 117.7, 117.7, 114.3, 113.7, 12.2. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{12}N_2O_1$ $[M+H]^+$: 225.1028, found 225.1026.



87

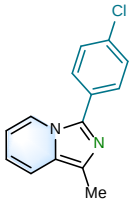
***N,N*-dimethyl-4-(1-methylimidazo[1,5-a]pyridin-3-yl)aniline:** Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), (*E*)-3-(4-(dimethylamino)phenyl)acrylaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 4 days. Chitosan was dried at 100 ºC overnight. Work-up gave product **87** (10.5 mg, 0.038 mmol, isolated yield 38%) as a yellow solid; **m.p.** 57−59 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.8 Hz, 1H), 7.52 (d, *J* = 16.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 1H), 6.88 (d, *J* = 15.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.51 – 6.42 (m, 2H), 2.92 (s, 6H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.3, 135.9, 130.4, 129.7, 129.2, 127.7, 125.3, 120.5, 118.4, 116.5, 112.7, 112.3, 107.6, 40.4, 12.6. **ESI-HRMS**: m/z calcd. for $C_{18}H_{19}N_3$ $[M+H]^+$: 278.1652, found 278.1654.



14

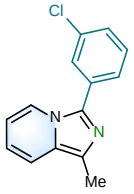
3-(4-fluorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-fluorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **14** (17.6 mg, 0.078 mmol, isolated yield 78%) as a yellow solid. **m.p.**: 82−83 ºC. Following the **General procedure C3**, a mixture of 2-acetylpyridine (0.1 mmol), 4-fluorobenzaldehyde (2.0 equiv.) and chitin (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC overnight. Work-up gave product **14** (16.0 mg, 0.071 mmol, isolated yield 71%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.2 Hz, 1H), 7.67 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.33 (d, *J* = 9.2 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.56 (dd, *J* = 9.2, 6.0 Hz, 1H), 6.45 – 6.42 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{C\text{-}F}$ = 247.1 Hz), 135.5, 129.7 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 128.7, 127.9, 126.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz), 120.8, 118.4, 117.1, 116.1 (d, $^2J_{C\text{-}F}$ = 21.6 Hz), 113.1, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}FN_2$ $[M+H]^+$: 227.0985, found 227.0980.



15

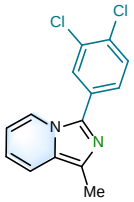
3-(4-chlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-chlorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **15** (17.7 mg, 0.073 mmol, isolated yield 73%) as a yellow solid. **m.p**: 63−64 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 10.0 Hz, 1H), 6.57 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.47 – 6.43 (m, 1H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.3, 134.2, 129.2, 129.1, 128.9, 128.8, 128.2, 121.6, 120.9, 118.4, 117.3, 113.3, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}ClN_2$ $[M+H]^+$: 243.0689, found 243.0687.



16

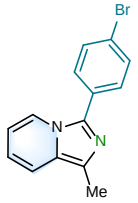
3-(3-chlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 3-chlorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **16** (17.0 mg, 0.070 mmol, isolated yield 70%) as a brown solid. **m.p**: 70−71 ºC. Following the **General procedure C3**, a mixture of 2-acetylpyridine (0.1 mmol), 3-chlorobenzaldehyde (2.0 equiv.) and chitin (3.0 equiv.) in the CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC oven overnight. Work-up gave product **15** (12.8 mg, 0.053 mmol, isolated yield 53%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.30 (m, 3H), 6.59 (dd, *J* = 9.2, 6.0 Hz, 1H), 6.50 – 6.46 (m, 1H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.9, 132.1, 130.2, 130.0, 129.3, 128.4, 128.3, 127.6, 125.6, 121.0, 118.5, 117.5, 113.4, 12.5. **ESI-HRMS**: m/z calcd. for $C_{14}H_{11}ClN_2$ $[M+H]^+$: 243.0689, found 243.0687.



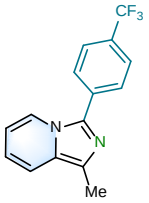
17

3-(3,4-dichlorophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 3,4-dichlorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **17** (15.7 mg, 0.057 mmol, isolated yield 57%) as a yellow solid. **m.p.**: 116−117 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 1H), 7.82 (s, 1H), 7.57 – 7.45 (m, 2H), 7.34 (d, *J* = 9.2 Hz, 1H), 6.61 – 6.58 (m, 1H), 6.50 – 6.47 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.0, 133.2, 132.0, 130.8, 130.4, 129.6, 129.2, 128.6, 126.4, 120.8, 118.5, 117.6, 113.6, 12.5. **ESI-HRMS**: m/z calcd. for $C_{14}H_{10}Cl_2N_2$ $[M+H]^+$: 277.0299, found 277.0295.



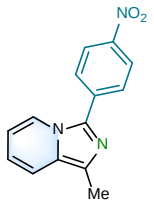
18

3-(4-bromophenyl)-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-bromobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **18** (18.31 mg, 0.064 mmol, isolated yield 64%) as a yellow solid. **m.p.**: 90−91 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 8.03 (m, 1H), 7.58 – 7.53 (m, 4H), 7.34 – 7.31 (m, 1H), 6.57 (dd, *J* = 9.1, 6.4 Hz, 1H), 6.47 – 6.43 (m, 1H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.3, 132.1, 129.2, 129.1, 129.1, 128.2, 122.3, 120.9, 118.4, 117.3, 113.3, 12.4. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}BrN_2$ $[M+H]^+$: 287.0184, found 287.0181.



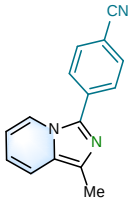
19

1-methyl-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-trifluoromethylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **19** (18.49 mg, 0.067 mmol, isolated yield 67%) as a yellow solid. **m.p.**: 72−73 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 – 8.12 (m, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.69 – 7.66 (m, 2H), 7.38 – 7.35 (m, 1H), 6.64 – 6.59 (m, 1H), 6.52 – 6.47 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.9, 133.9 (q, $^4J_{C\text{-}F}$ = 1.2 Hz), 129.8 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 129.8, 128.7, 127.6, 125.9 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 270.4 Hz), 120.9, 118.5, 117.7, 113.6, 12.5. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.6. **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}F_3N_2$ $[M+H]^+$: 277.0953, found 277.0950.



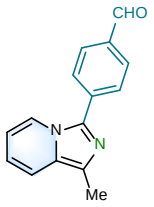
20

1-methyl-3-(4-nitrophenyl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-nitrobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **20** (10.6 mg, 0.042 mmol, isolated yield 42%) as a red solid. **m.p.**: 142−143 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.8 Hz, 2H), 8.22 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 9.2 Hz, 1H), 6.71 – 6.67 (m, 1H), 6.61 – 6.57 (m, 1H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.6, 136.5, 134.0, 131.0, 129.6, 127.3, 124.4, 121.0, 118.7, 118.4, 114.3, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}N_3O_2$ $[M+H]^+$: 254.0930, found 254.0926.



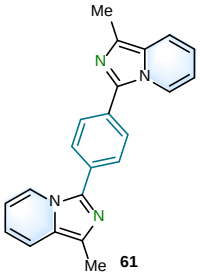
21

4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzonitrile: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 4-formylbenzonitrile (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **21** (8.4 mg, 0.036 mmol, isolated yield 36%) as a yellow solid. **m.p.**: 89−90 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 1H), 6.66 (dd, *J* = 8.9, 6.5 Hz, 1H), 6.57 – 6.54 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.6, 134.3, 132.7, 130.5, 129.2, 127.4, 120.9, 118.7, 118.6, 118.1, 114.0, 111.0, 12.5. **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}N_3$ $[M+H]^+$: 234.1031, found 234.1030.



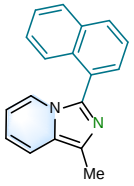
23

4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzaldehyde: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), terephthalaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **23** (12.5 mg, 0.053 mmol, isolated yield 53%) as a yellow solid. **m.p.**: 310−312 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 7.92 (s, 4H), 7.38 (d, *J* = 8.8 Hz, 1H), 6.65 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.54 (t, *J* = 6.8 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 191.5, 136.0, 135.3, 135.0, 130.4, 130.3, 129.1, 127.4, 121.2, 118.6, 118.0, 113.9, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{12}N_2O$ $[M+H]^+$: 237.1028, found 237.1024.



61

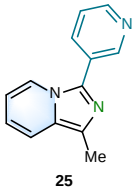
1,4-bis(1-methylimidazo[1,5-a]pyridin-3-yl)benzene: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), terephthalaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 4 days. Chitosan was dried at 100 ºC overnight. Work-up gave product **61** (8.1 mg, 0.024 mmol, isolated yield 24%) as a brown red solid. **m.p.**: 212−214 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.2 Hz, 2H), 7.86 (s, 4H), 7.35 (d, *J* = 9.3 Hz, 2H), 6.58 (dd, *J* = 9.0, 6.3 Hz, 2H), 6.49 – 6.44 (m, 2H), 2.52 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.0, 130.1, 129.3, 128.3, 128.0, 121.2, 118.4, 117.2, 113.2, 12.6. **ESI-HRMS**: m/z calcd. for $C_{22}H_{18}N_4$ $[M+H]^+$: 338.1531, found 338.1526.



24

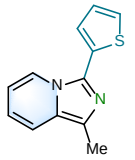
1-methyl-3-(naphthalen-1-yl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 1-naphthaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried under 100 ºC overnight. Work-up gave product **24** (8.0 mg, 0.031 mmol, isolated yield 31%) as a brown solid. **m.p.**: 90−93 ºC. Following the **General procedure C3**, a mixture of 2-acetylpyridines (0.1 mmol), 1-naphthaldehyde (2.0 equiv.) and chitin (3.0 equiv.) in the CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC oven overnight. Work-up gave product **24** (7.5 mg, 0.029 mmol, isolated yield 29%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 2H), 7.66 – 7.62 (m, 2H), 7.53 – 7.48 (m, 2H), 7.44 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.41 – 7.35 (m, 2H), 6.57 (dd, *J* = 9.0, 6.0 Hz, 1H), 6.35 – 6.30 (m, 1H), 2.57 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.3, 133.9, 131.8, 129.6, 128.8, 128.5, 128.5, 127.5, 127.4, 126.9, 126.2, 125.7, 125.3, 121.6, 118.1, 117.0, 112.3, 12.7. **ESI-HRMS**: m/z calcd. for $C_{18}H_{14}N_2$ $[M+H]^+$: 259.1235, found 259.1233.



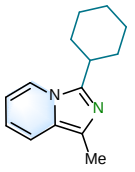
25

1-methyl-3-(pyridin-3-yl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), nicotinaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **25** (12.1 mg, 0.058 mmol, isolated yield 58%) as a brown liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.56 (d, *J* = 4.4 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.64 – 6.60 (m, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.0, 148.2, 135.2, 133.3, 129.8, 128.6, 126.8, 123.8, 120.7, 118.5, 117.7, 113.7, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{11}N_3$ $[M+H]^+$: 210.1031, found 210.1027.



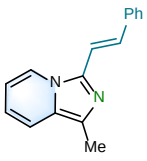
26

1-methyl-3-(thiophen-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), thiophene-2-carbaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **26** (5.8 mg, 0.027 mmol, isolated yield 27%) as a brown solid. **m.p.**: 79−81 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.8 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.35 – 7.30 (m, 2H), 7.09 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.60 – 6.56 (m, 1H), 6.54 – 6.50 (m, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.7, 131.3, 129.3, 128.2, 127.6, 125.5, 124.0, 121.5, 118.4, 117.0, 113.5, 12.6. **ESI-HRMS**: *m/z* calcd. for $C_{12}H_{10}N_2S$ $[M+H]^+$: 215.0643, found 215.0641.



28

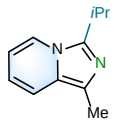
3-cyclohexyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), cyclohexanecarbaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **28** (14.8 mg, 0.069 mmol, isolated yield 69%) as a colorless solid. **m.p.**: 92−93 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.22 (dd, *J* = 9.2 Hz, 0.8 Hz, 1H), 6.45 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.39 – 6.35 (m, 1H), 2.85 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.42 (s, 3H), 1.92 (d, *J* = 13.2 Hz, 2H), 1.83 (d, *J* = 12.8 Hz, 2H), 1.71 – 1.68 (m, 3H), 1.37 – 1.29 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.2, 126.2, 126.1, 120.2, 118.3, 115.9, 111.9, 35.7, 30.8, 26.4, 25.9, 12.2. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{18}N_2$ $[M+H]^+$: 215.1548, found 215.1544.



30

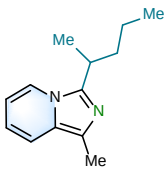
(*E*)-1-methyl-3-styrylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), cinnamaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **30** (6.6 mg, 0.028 mmol, isolated yield 28%) as a brown solid. **m.p.**: 110−111 ºC. Following the **General procedure C3**, a mixture of 2-acetylpyridine (0.1 mmol), cinnamaldehyde (2.0 equiv.) and chitin (3.0 equiv.) in the CF_3COOH (0.1 M) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC overnight. Work-up gave product **30** (4.0 mg, 0.017 mmol, isolated yield 17%) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.31 – 7.28 (m, 3H), 7.21 – 7.18 (m, 2H), 6.58 – 6.49 (m, 2H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.1, 129.6, 128.7, 127.8, 126.5, 120.5, 118.5, 117.1, 113.2, 112.0, 12.7. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{14}N_2$ $[M+H]^+$: 235.1235, found 235.1229.



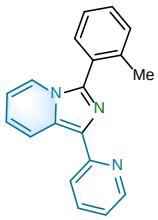
31

3-isopropyl-1-methylimidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), isobutyraldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **31** (8.7 mg, 0.050 mmol, isolated yield 50%) as a brown solid. **m.p.**: 93−95 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 9.3 Hz, 1H), 6.46 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.40 – 6.35 (m, 1H), 3.21 (hept, *J* = 6.9 Hz, 1H), 2.43 (s, 3H), 1.36 (d, *J* = 6.9 Hz, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.8, 126.4, 120.2, 118.3, 115.6, 111.7, 25.9, 20.5, 12.5. **ESI-HRMS**: *m/z* calcd. for $C_{11}H_{14}N_2$ $[M+H]^+$: 175.1235, found 175.1227.



33

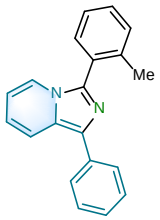
1-methyl-3-(pentan-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure C1**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylpentanal (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOH (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **33** (10.5 mg, 0.052 mmol, isolated yield 52%) as a brown liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 6.50 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.44 – 6.40 (m, 1H), 3.15 (h, *J* = 7.0 Hz, 1H), 2.48 (s, 3H), 1.93 – 1.85 (m, 1H), 1.73 – 1.65 (m, 1H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.23 – 1.13 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.4, 126.4, 126.1, 120.1, 118.2, 115.6, 111.7, 37.6, 30.9, 20.6, 18.6, 14.0, 12.3. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{18}N_2$ $[M+H]^+$: 203.1548, found 203.1543.



35

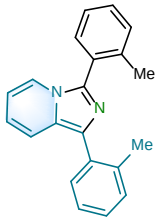
1-(pyridin-2-yl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **35** (18.5 mg, 0.065 mmol, isolated yield 65%) as a yellow solid. **m.p.**: 90−91 ºC. Following the **General procedure C4**, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitin (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried under 100 ºC overnight. Work-up gave product **35** (7.4 mg, 0.026 mmol, isolated yield 26%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 9.2 Hz, 1H), 8.65 (d, *J* = 4.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.11 – 7.08 (m, 1H), 6.94 – 6.90 (m, 1H), 6.59 (t, *J* = 6.8 Hz, 1H), 2.28 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 148.9, 138.4, 137.6, 136.1, 130.7, 130.5, 129.8, 129.5, 129.1, 129.0, 126.0, 121.5, 121.5, 120.8, 120.2, 119.7, 113.5, 19.6. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$: 286.1344, found 286.1342.



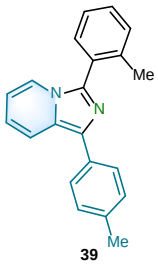
37

1-phenyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of phenyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **37** (20.2 mg, 0.071 mmol, isolated yield 71%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.32 – 7.28 (m, 2H), 7.26 – 7.16 (m, 2H), 6.72 – 6.68 (m, 1H), 6.45 – 6.41 (m, 1H), 2.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 137.8, 135.1, 131.1, 130.8, 130.6, 129.5, 129.2, 128.6, 126.6, 126.3, 126.1, 121.9, 119.5, 118.9, 112.8, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{16}N_2$ $[M+H]^+$: 285.1392, found 285.1390.



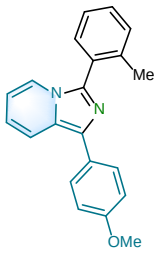
38

1,3-di-o-tolylimidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of pyridin-2-yl(o-tolyl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **38** (16.1 mg, 0.054 mmol, isolated yield 54%) as a green solid. **m.p.**: 112−113 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 1H), 7.45 – 7.39 (m, 3H), 7.31 (d, *J* = 2.8 Hz, 2H), 7.27 – 7.23 (m, 2H), 7.21 – 7.18 (m, 2H), 6.67 – 6.64 (m, 1H), 6.49 – 6.44 (m, 1H), 2.41 (s, 3H), 2.24 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 137.3, 130.9, 130.8, 130.3, 130.2, 129.5, 127.4, 126.0, 125.5, 121.5, 118.9, 112.9, 20.7, 19.9. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2$ $[M+H]^+$: 299.1548, found 299.1546.



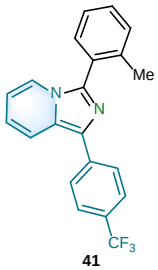
39

3-(o-tolyl)-1-(p-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of pyridin-2-yl(p-tolyl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **39** (20.2 mg, 0.083 mmol, isolated yield 68%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 3H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.18 (m, 5H), 6.69 (dd, *J* = 9.3, 6.3 Hz, 1H), 6.45 – 6.42 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 137.6, 136.0, 132.2, 131.2, 130.8, 130.6, 129.5, 129.4, 129.3, 126.5, 126.3, 126.1, 121.8, 119.2, 119.1, 112.7, 21.2, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2$ $[M+H]^+$: 299.1548, found 299.1544.



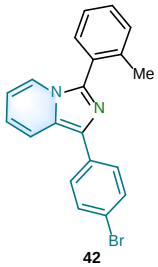
40

1-(4-methoxyphenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of (4-methoxyphenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **40** (22.9 mg, 0.073 mmol, isolated yield 73%) as a yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2H), 7.73 (d, *J* = 9.3 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.23 (m, 3H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.68 (ddd, *J* = 9.3, 6.3, 0.9 Hz, 1H), 6.45 – 6.41 (m, 1H), 3.79 (s, 3H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 137.3, 130.9, 130.8, 130.3, 130.2, 129.5, 127.4, 126.0, 125.5, 121.5, 118.9, 112.9, 20.7, 19.9. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{18}N_2O$ $[M+H]^+$: 315.1497, found 315.1495.



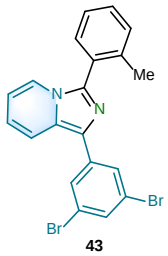
41

3-(o-tolyl)-1-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of pyridin-2-yl(4-(trifluoromethyl)phenyl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **41** (28.5 mg, 0.081 mmol, isolated yield 81%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.26 (m, 3H), 6.82 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.54 – 6.50 (m, 1H), 2.19 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.7, 138.5, 138.4, 131.2, 130.9, 130.6, 129.8, 129.5, 128.9, 127.9 (q, $^2J_{C\text{-}F}$ = 33.4 Hz), 127.4, 126.3, 126.2, 125.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.5 (q, $^1J_{C\text{-}F}$ = 270.1 Hz), 122.3, 120.8, 118.6, 113.1, 19.8. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.2. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{15}F_3N_2$ $[M+H]^+$: 353.1266, found 353.1261.



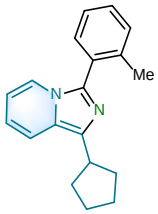
42

1-(4-bromophenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of (4-bromophenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **42** (27.1 mg, 0.075 mmol, isolated yield 75%) as a yellow solid. **m.p.**: 123−124 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 3H), 7.55 (d, *J* = 6.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.34 – 7.26 (m, 3H), 6.78 – 6.74 (m, 1H), 6.50 – 6.47 (m, 1H), 2.18 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.5, 138.0, 134.1, 131.7, 130.9, 130.6, 129.8, 129.7, 128.0, 126.7, 126.2, 122.1, 120.1, 120.0, 118.7, 113.0, 19.8. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{15}BrN_2$ $[M+H]^+$: 363.0497, found 363.0494.



43

1-(3,5-dibromophenyl)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of (3,5-dibromophenyl)(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **43** (28.2 mg, 0.064 mmol, isolated yield 64%) as a yellow solid. **m.p.**: 138−140 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.98 (m, 2H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.47 (dt, *J* = 3.2, 1.7 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.36 – 7.26 (m, 3H), 6.87 – 6.82 (m, 1H), 6.55 – 6.51 (m, 1H), 2.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.7, 138.5, 138.4, 131.3, 130.9, 130.6, 129.9, 128.7, 127.9, 127.7, 127.4, 126.2, 123.2, 122.3, 121.1, 118.4, 113.2, 19.7. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{14}Br_2N_2$ $[M+H]^+$: 440.9602, found 440.9609.

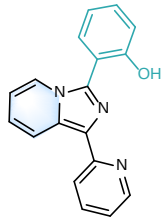


44

1-cyclopentyl-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of cyclopentyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **44** (25.36 mg, 0.092 mmol, isolated yield 92%) as a brown solid. **m.p.**: 72−73 ºC. Following the **General procedure C4**, a mixture of cyclopentyl(pyridin-2-yl)methanone (0.1 mmol), 2-methylbenzoaldehyde (4.0 equiv.) and chitin (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC overnight. Work-up gave product **44** (24.6 mg, 0.089 mmol, isolated yield 89%) as a brown solid.

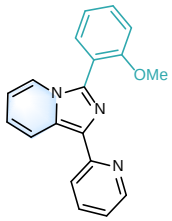
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 9.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.20 – 7.16 (m, 1H), 6.49 (ddd, *J* = 9.2, 6.3, 0.8 Hz, 1H), 6.34 – 6.30 (m, 1H), 3.37 –

3.28 (m, 1H), 2.10 (s, 3H), 2.04 – 1.99 (m, 2H), 1.91 – 1.87 (m, 2H), 1.81 – 1.78 (m, 2H), 1.64 – 1.60 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.4, 136.1, 135.9, 130.7, 130.4, 129.5, 129.2, 125.9, 125.8, 121.2, 118.2, 116.5, 112.3, 38.3, 33.4, 25.7, 19.6. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{20}N_2$ $[M+H]^+$: 277.1705, found 277.1703.



46

2-(1-(pyridin-2-yl)imidazo[1,5-a]pyridin-3-yl)phenol: Following the **General procedure C2**, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-hydroxybenzaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **46** (5.2 mg, 0.085 mmol, isolated yield 18%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 9.2 Hz, 1H), 8.57 (d, *J* = 4.0 Hz, 1H), 8.48 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.67 (td, *J* = 7.8, 2.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.12 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.06 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.72 – 6.68 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 153.9, 149.1, 136.4, 135.5, 130.1, 129.6, 128.6, 124.5, 122.3, 122.3, 121.7, 120.9, 119.8, 119.1, 117.8, 114.8, 114.0. The compound is known, and the NMR data is in accordance with the previous literature.[330]

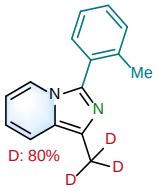


47

3-(2-methoxyphenyl)-1-(pyridin-2-yl)imidazo[1,5-a]pyridine: Following the **General procedure C2**, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-methoxybenzaldehyde (4.0 equiv.) and chitosan (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **47** (13.3 mg, 0.044 mmol, isolated yield 44%) as a yellow solid. Following the **General procedure C4**, a mixture of di(pyridin-2-yl)methanone (0.1 mmol), 2-

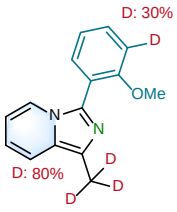
methoxybenzaldehyde (4.0 equiv.) and chitin (2.5 equiv.) in CF_3COOH (0.7 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitin was dried at 100 ºC overnight. Work-up gave product **47** (4.8 mg, 0.016 mmol, isolated yield 16%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 9.2 Hz, 1H), 8.56 – 8.54 (m, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.08 – 7.05 (m, 1H), 7.01 – 6.97 (m, 2H), 6.86 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.55 – 6.52 (m, 1H), 3.73 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.6, 155.3, 148.9, 136.1, 132.8, 131.0, 130.1, 130.0, 123.3, 121.2, 121.2, 120.9, 120.2, 119.9, 119.1, 112.7, 111.2, 55.6. The compound is known, and the NMR data is in accordance with the previous literature.[226]



66

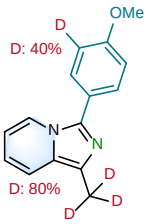
1-(methyl-d_3)-3-(o-tolyl)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **66** (16.4 mg, 0.073 mmol, isolated yield 73%) as a yellow solid. **m.p.** 62−64 °C. D incorporation by ^{1}H NMR: 80%. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.37 – 7.19 (m, 5H), 6.53 (dd, *J* = 9.1, 6.3 Hz, 1H), 6.37 – 6.32 (m, 1H), 2.48 (s, 0.59H), 2.13 (s, 3H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{11}D_3N_2$ $[M+H]^+$: 226.1424, found 226.1420.



70

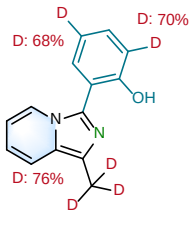
3-(2-3-(2-methoxyphenyl-3-d)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 2-methoxybenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan

was dried at 100 ºC overnight. Work-up gave product **70** (14.7 mg, 0.061 mmol, isolated yield 61%) as a yellow solid; **m.p.** 44−46 °C. D incorporation by ^{1}H NMR: 80% and 30%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.45 – 7.43 (m, 1H), 7.37 – 7.31 (m, 2H), 7.04 – 7.00 (m, 0.70H), 6.96 (dd, *J* = 8.4, 4.4 Hz, 1H), 6.57 – 6.53 (m, 1H), 6.40 – 6.35 (m, 1H), 3.73 (s, 3H), 2.49 (s, 0.59H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{10}D_4N_2O$ $[M+H]^+$: 243.1435, found 243.1422.



71

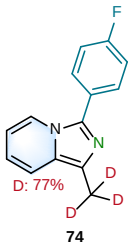
3-(4-methoxyphenyl-3-d)-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 4-methoxybenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **71** (15.2 mg, 0.063 mmol, isolated yield 63%) as a yellow solid. D incorporation by ^{1}H NMR: 80% and 40%. **m.p.** 43−45 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 9.2 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 1.59H), 6.51 (ddd, *J* = 9.2, 6.4, 0.8 Hz, 1H), 6.38 (ddd, *J* = 7.6, 6.4, 1.2 Hz, 1H), 3.80 (s, 3H), 2.46 (s, 0.60H). **ESI-HRMS**: m/z calcd. for $C_{15}H_{10}D_4N_2O$ $[M+H]^+$: 243.1435, found 243.1422.



73

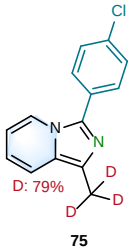
2-(1-(methyl-d_3)imidazo[1,5-a]pyridin-3-yl)phen-4,6-d_2-ol: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 2-hydroxybenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **73** (6.9 mg, 0.030 mmol, isolated yield 30%) as a white solid. **m.p.** 130−132 °C. D incorporation by ^{1}H NMR: 76%, 70% and 68%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.0, 3.6 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.38 – 7.34 (m, 1H), 7.19 (d, *J* = 4.4 Hz, 1H), 7.07 (dd, *J* = 8.0,

4.0 Hz, 0.32H), 6.93 – 6.88 (m, 0.30H), 6.65 – 6.60 (m, 1H), 6.56 – 6.51 (m, 1H), 2.46 (s, 0.73H). **ESI-HRMS**: m/z calcd. for $C_{14}H_7D_5N_2O$ $[M+H]^+$: 230.1342, found 230.1330.



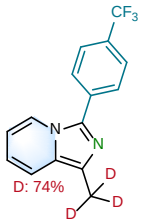
74

3-(4-fluorophenyl)-1-(methyl-d$_3$)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 4-fluorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **74** (16.9 mg, 0.074 mmol, isolated yield 74%) as a yellow solid. D incorporation by ^{1}H NMR: 77%. **m.p.** 93−95 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 1H), 7.67 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.54 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.44 – 6.40 (m, 1H), 2.46 (s, 0.68H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_2F$ $[M+H]^+$: 230.1173, found 230.1168.



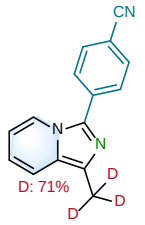
75

3-(4-chlorophenyl)-1-(methyl-d$_3$)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 4-chlorobenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **75** (18.6 mg, 0.076 mmol, isolated yield 76%) as a yellow solid. D incorporation by ^{1}H NMR: 79%. **m.p.** 84−86 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 1H), 6.60 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.50 – 6.46 (m, 1H), 2.47 (s, 0.62H). **ESI-HRMS**: m/z calcd. for $C_{14}H_8D_3N_2Cl$ $[M+H]^+$: 246.0877, found 246.0873.



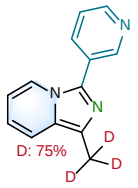
79

1-(methyl-d_3)-3-(4-(trifluoromethyl)phenyl)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 4-trifluoromethylbenzaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product 7**9** (18.1 mg, 0.065 mmol, isolated yield 65%) as a yellow solid. D incorporation by ^{1}H NMR: 74%. **m.p.** 69−71 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 9.3 Hz, 1H), 6.63 – 6.58 (m, 1H), 6.51 – 6.46 (m, 1H), 2.47 (s, 0.77H). **ESI-HRMS**: m/z calcd. for $C_{15}H_8D_3F_3N_2$ $[M+H]^+$: 280.1141, found 280.1137.



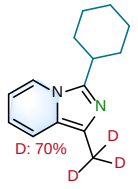
80

4-(1-methylimidazo[1,5-a]pyridin-3-yl)benzonitrile: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), 4-formylbenzonitrile (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **80** (7.8 mg, 0.033 mmol, isolated yield 33%) as a yellow solid. D incorporation by ^{1}H NMR: 71%. **m.p.** 120−122 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.5 Hz, 1H), 7.85 (q, *J* = 8.4 Hz, 4H), 7.36 (d, *J* = 9.9 Hz, 1H), 6.64 – 6.59 (m, 1H), 6.52 – 6.48 (m, 1H), 2.48 (s, 0.86H). **ESI-HRMS**: m/z calcd. for $C_{15}H_8D_3N_3$ $[M+H]^+$: 237.1220, found 237.1219.



83

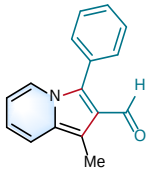
1-(methyl-d_3)-3-(pyridin-3-yl)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), nicotinaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **83** (12.72 mg, 0.060 mmol, isolated yield 60%) as a yellow solid. D incorporation by ^{1}H NMR: 75%. **m.p.** 45−47 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.56 – 8.54 (m, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 2H), 6.63 – 6.59 (m, 1H), 6.51 – 6.47 (m, 1H), 2.47 (s, 0.75H). **ESI-HRMS**: m/z calcd. for $C_{13}H_8D_3N_3$ $[M+H]^+$: 213.1220, found 213.1213.



88

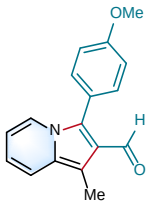
3-cyclohexyl-1-(methyl-d_3)imidazo[1,5-a]pyridine: Following the **General procedure C5**, a mixture of 2-acetylpyridine (0.1 mmol), cyclohexanecarbaldehyde (2.0 equiv.) and chitosan (3.0 equiv.) in CF_3COOD (1.0 mL) was stirred at 140 ºC under Ar atmosphere for 36 h. Chitosan was dried at 100 ºC overnight. Work-up gave product **88** (13.9 mg, 0.064 mmol, isolated yield 64%) as a white solid. D incorporation by ^{1}H NMR: 70%. **m.p.** 74−76 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.45 – 6.32 (m, 2H), 2.39 (s, 0.90H), 1.94 – 1.64 (m, 8H), 1.37 – 1.31 (m, 3H). **ESI-HRMS**: m/z calcd. for $C_{14}H_{15}D_3N_2$ $[M+H]^+$: 218.1737, found 218.1736.

5.3.4 Anomeric stereoauxiliary-organocatalyzed one-pot site-selective C_2-aldehylation for trisubstituted indolizine-2-carbaldehydes



91

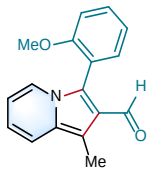
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehydes (0.2 mmol), heteroaryl ketones (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-methyl-3-phenylindolizine-2-carbaldehyde (**91,** 44.7 mg, 0.19 mmol, isolated yield 95%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3052, 2922, 2749, 1661, 1517, 1477, 1430, 1383, 1358, 1319, 1247, 1218, 1142, 1115, 1076, 997, 940, 872, 830, 756, 736, 715, 699, 682, 666, 620, 534, 482, 431. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.42 – 7.40 (m, 3H), 7.32 (d, *J* = 9.2 Hz, 1H), 6.61 – 6.56 (m, 1H), 6.40 – 6.36 (m, 1H), 2.53 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.7, 131.3, 131.0, 130.6, 129.0, 128.9, 128.8, 123.4, 122.3, 119.1, 117.6, 112.7, 109.9, 9.7. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{13}NO$ $[M+H]^+$: 236.1075, found 236.1071.



92

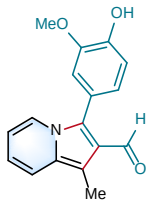
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-methoxyphenyl)-1-methylindolizine-2-carbaldehyde (**92,** 33.4 mg, 0.13 mmol, isolated yield 63%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2922, 2840, 2741, 1661, 1607, 1574, 1527, 1482, 1432, 1381, 1356, 1319, 1286, 1245, 1220, 1175, 1150, 1111, 1026, 878, 824, 785, 736, 684, 641, 626, 583, 515, 433, 404. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.34 – 7.28 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.57 – 6.53 (m, 1H), 6.35 (t, *J* = 6.6 Hz, 1H), 3.81 (s, 3H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$)

δ 189.7, 160.1, 132.2, 131.4, 130.3, 123.3, 122.3, 120.8, 119.0, 117.4, 114.5, 112.5, 109.6, 55.4, 9.6. **ESI-HRMS**: *m/z* calcd. for $C_{17}H_{15}NO_2$ $[M+H]^+$: 266.1181, found 266.1177.



93

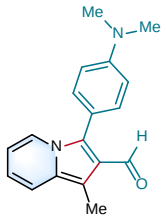
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(2-methoxyphenyl)-1-methylindolizine-2-carbaldehyde (**93**, 50.4 mg, 0.19 mmol, isolated yield 95%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2920, 2833, 2745, 1663, 1601, 1576, 1515, 1463, 1432, 1383, 1358, 1321, 1288, 1278, 1245, 1216, 1181, 1152, 1146, 1127, 1100, 1047, 1022, 940, 880, 851, 835, 783, 736, 713, 684, 659, 573, 552, 528, 462, 429. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.43 – 7.38 (m, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.25 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.03 – 6.98 (m, 2H), 6.57 (dd, *J* = 9.1, 6.3 Hz, 1H), 6.36 (t, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.7, 157.9, 133.7, 130.8, 128.2, 123.6, 123.4, 120.7, 118.8, 117.4, 117.2, 112.0, 111.2, 109.5, 55.5, 9.7. **ESI-HRMS**: *m/z* calcd. for $C_{17}H_{15}NO_2$ $[M+H]^+$: 266.1181, found 266.1176.



94

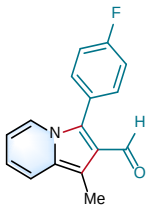
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-hydroxy-3-methoxyphenyl)-1-methylindolizine-2-carbaldehyde (**94**, 36.5 mg, 0.13 mmol, isolated yield 63%) as a yellow solid. **mp**: 168−169 ˚C. **FT-IR**: *v* (cm^{-1}): 3171, 2924, 2852, 1638, 1583, 1523, 1488, 1471, 1432, 1416, 1377, 1344, 1319, 1271, 1236, 1208, 1177, 1142, 1125, 1057, 1030, 964, 913, 888, 876, 812, 769, 736, 725, 684, 659, 647, 571, 558, 528, 517, 433, 410. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.92 (s,

1H), 7.74 (d, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.58 – 6.54 (m, 1H), 6.37 (t, *J* = 6.8 Hz, 1H), 5.83 (s, 1H), 3.84 (s, 3H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.8, 146.9, 146.5, 131.6, 130.3, 124.4, 123.3, 122.5, 120.5, 119.1, 117.4, 115.0, 113.4, 112.6, 109.6, 56.1, 9.6. **ESI-HRMS**: *m/z* calcd. for $C_{17}H_{15}NO_3$ $[M+H]^+$: 282.1130, found 282.1124.



95

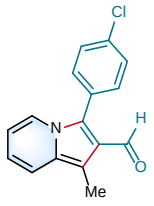
Following the **General procedure D2**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), and $LiSO_3CF_3$ (3.0 equiv.) in the AcOH : CF_3CH_2OH (0.4 : 0.5 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. Work-up gave product 3-(4-(dimethylamino)phenyl)-1-methylindolizine-2-carbaldehyde (**95**, 25.0 mg, 0.09 mmol, isolated yield 46%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2924, 2854, 2800, 1661, 1605, 1531, 1488, 1432, 1352, 1222, 1195, 1164, 1113, 1057, 944, 876, 814, 736, 641, 552, 515, 435. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.25 (m, 4H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.53 (dd, *J* = 9.0, 6.4 Hz, 1H), 6.33 (t, *J* = 6.6 Hz, 1H), 2.98 (s, 6H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.2, 150.6, 132.8, 131.8, 130.1, 123.1, 122.6, 119.0, 117.2, 115.7, 112.2, 112.2, 109.3, 40.3, 9.7. **ESI-HRMS**: m/z calcd. for $C_{18}H_{18}N_2O$ [M+H]+: 279.1497, found 279.1502.



96

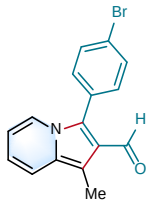
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-fluorophenyl)-1-methylindolizine-2-carbaldehyde (**96**, 40.5 mg, 0.16 mmol, isolated yield 81%) as a

yellow liquid. **FT-IR**: *v* (cm^{-1}): 3072, 2924, 2739, 1665, 1601, 1525, 1480, 1434, 1383, 1356, 1319, 1220, 1158, 1113, 1094, 1053, 938, 878, 828, 802, 736, 717, 684, 641, 571, 550, 509, 441, 420. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.15 (t, *J* = 8.6 Hz, 2H), 6.57 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.40 – 6.37 (m, 1H), 2.51 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.2, 163.0 (d, $^{1}J_{C\text{-}F}$ = 248.2 Hz), 132.8 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 130.6, 129.8, 124.9 (d, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 123.4, 122.1, 119.1, 117.6, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 112.9, 110.0, 9.5. **^{19}F NMR** (375 MHz, $CDCl_3$) δ -111.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{12}NOF$ $[M+H]^+$: 254.0981, found 254.0975.



97

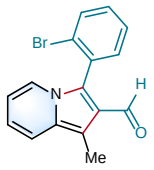
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-chlorophenyl)-1-methylindolizine-2-carbaldehyde (**97**, 40.4 mg, 0.15 mmol, isolated yield 75%) as a yellow solid. **mp**: 105−106 ˚C. **FT-IR**: *v* (cm^{-1}): 3056, 2916, 2846, 1655, 1510, 1475, 1430, 1405, 1385, 1352, 1319, 1247, 1220, 1150, 1111, 1090, 1014, 938, 878, 820, 740, 729, 711, 680, 637, 622, 548, 536, 501, 482, 435, 404. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.31 (m, 3H), 6.61 – 6.57 (m, 1H), 6.40 (t, *J* = 6.8 Hz, 1H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.1, 135.1, 132.1, 130.8, 129.4, 127.3, 123.4, 122.0, 119.2, 117.7, 113.1, 110.3, 9.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{13}ClNO$ $[M+H]^+$: 270.0686, found 270.0685.



98

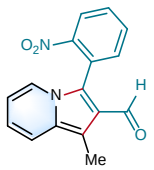
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the

CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-bromophenyl)-1-methylindolizine-2-carbaldehyde (**98**, 53.2 mg, 0.17 mmol, isolated yield 87%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2916, 2747, 1663, 1587, 1508, 1471, 1432, 1399, 1381, 1354, 1321, 1249, 1220, 1148, 1115, 1069, 1010, 938, 878, 814, 736, 680, 666, 622, 560, 534, 492, 433, 402. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 9.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.58 (dd, J = 9.2, 6.6 Hz, 1H), 6.41 – 6.37 (m, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.0, 132.3, 132.3, 130.8, 129.3, 127.8, 123.3, 123.2, 122.0, 119.1, 117.7, 113.1, 110.3, 9.5. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{12}NOBr$ $[M+H]^+$: 314.0181, found 314.0164.



99

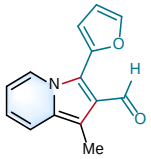
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(2-bromophenyl)-1-methylindolizine-2-carbaldehyde (**99**, 43.8 mg, 0.14 mmol, isolated yield 71%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2918, 2850, 2807, 2739, 1667, 1510, 1432, 1385, 1358, 1321, 1249, 1218, 1154, 1144, 1125, 1115, 1045, 1024, 954, 882, 861, 833, 754, 736, 711, 688, 645, 569, 550, 536, 497, 447, 420. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.69 – 7.67 (m, 1H), 7.38 – 7.27 (m, 5H), 6.61 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.44 – 6.40 (m, 1H), 2.54 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.8, 134.2, 133.3, 131.0, 130.7, 130.3, 129.2, 127.6, 125.9, 123.6, 122.8, 119.0, 117.6, 112.7, 109.6, 9.6. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{12}NOBr$ $[M+H]^+$: 314.0181, found 314.0164.



100

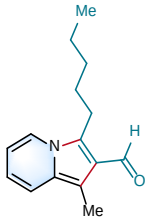
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-

methyl-3-(2-nitrophenyl)indolizine-2-carbaldehyde (**13**, 39.2 mg, 0.14 mmol, isolated yield 69%) as a red liquid. **FT-IR**: *v* (cm^{-1}): 2916, 2854, 1667, 1609, 1583, 1523, 1467, 1432, 1385, 1339, 1300, 1249, 1220, 1144, 995, 950, 936, 853, 830, 787, 738, 717, 701, 666, 647, 567, 536, 482, 422. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.15 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.68 (td, *J* = 7.2, 1.6 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.36 (d, *J* = 9.2 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 6.63 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.44 – 6.41 (m, 1H), 2.53 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.7, 149.7, 134.5, 133.4, 131.3, 130.5, 125.2, 124.5, 123.5, 123.4, 122.2, 119.2, 117.7, 113.6, 111.0, 9.1. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{12}N_2O_3$ $[M+H]^+$: 281.0926, found 281.0921.



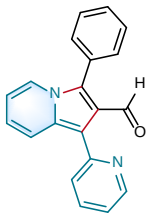
101

Following the **General procedure D3**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (4.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at room temperature under Ar atmosphere for 42 h. Work-up gave product 3-(furan-2-yl)-1-methylindolizine-2-carbaldehyde (**101**, 13.5 mg, 0.06 mmol, isolated yield 30%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3118, 2920, 2850, 1663, 1510, 1463, 1434, 1381, 1352, 1319, 1249, 1212, 1162, 1144, 1117, 1076, 1016, 958, 888, 874, 808, 7734, 682, 659, 620, 593, 528, 427. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 7.58 (s, 1H), 7.35 (d, *J* = 9.2 Hz, 1H), 6.68 – 6.64 (m, 1H), 6.61 (d, *J* = 3.2 Hz, 1H), 6.55 – 6.50 (m, 2H), 2.52 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.3, 143.6, 143.4, 131.5, 124.0, 124.0, 120.2, 119.0, 118.2, 113.3, 112.2, 111.6, 110.9, 9.6. **ESI-HRMS**: *m/z* calcd. for $C_{14}H_{11}NO_2$ $[M+H]^+$: 226.0868, found 226.0862.



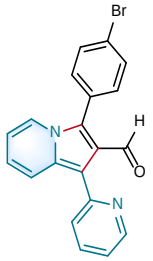
102

Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-methyl-3-pentylindolizine-2-carbaldehyde (**102**, 34.4 mg, 0.15 mmol, isolated yield 76%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2955, 2924, 2856, 2734, 1663, 1504, 1447, 1434, 1393, 1321, 1249, 1199, 1142, 1111, 1057, 905, 853, 732, 643, 523, 427. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 6.48 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.44 – 6.40 (m, 1H), 3.08 – 3.05 (m, 2H), 2.44 (s, 3H), 1.55 (p, *J* = 7.4 Hz, 2H), 1.29 – 1.25 (m, 4H), 0.80 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.0, 130.3, 129.7, 122.0, 121.6, 119.1, 115.9, 112.6, 109.8, 31.5, 27.8, 23.6, 22.4, 13.9, 8.9. **ESI-HRMS**: *m/z* calcd. for $C_{15}H_{19}NO$ $[M+H]^+$: 230.1545, found 230.1542.



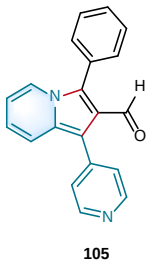
103

Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-phenyl-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**103**, 56.6 mg, 0.19 mmol, isolated yield 95%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3060, 2846, 2761, 1673, 1585, 1517, 1473, 1445, 1420, 1381, 1354, 1323, 1278, 1267, 1236, 1191, 1146, 1123, 1096, 1076, 1055, 1039, 1024, 987, 948, 923, 905, 824, 779, 740, 719, 694, 664, 645, 624, 610, 585, 565, 507, 486, 433, 406. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.61 (d, *J* = 4.8 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 3.2 Hz, 2H), 7.47 – 7.40 (m, 5H), 7.09 (q, *J* = 4.4 Hz, 1H), 6.74 (dd, *J* = 9.2, 6.5 Hz, 1H), 6.47 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.6, 153.2, 149.1, 135.7, 132.1, 131.6, 131.1, 129.2, 128.9, 128.7, 125.5, 122.7, 122.2, 120.9, 120.4, 114.0, 113.6. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{14}N_2O$ $[M+H]^+$: 299.1184, found 299.1180.



104

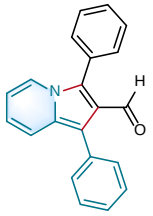
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-(4-bromophenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**104**, 63.9 mg, 0.17 mmol, isolated yield 83%) as a yellow solid. **mp**: 167−168 ˚C. **FT-IR**: *v* (cm^{-1}): 3052, 2854, 2770, 1671, 1630, 1585, 1562, 1519, 1506, 1469, 1434, 1397, 1333, 1263, 1232, 1193, 1148, 1107, 1094, 1074, 1051, 1037, 1008, 989, 946, 911, 841, 814, 775, 740, 725, 713, 686, 618, 563, 503, 495, 441, 404. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.66 (d, *J* = 3.6 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.65 – 7.63 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 1H), 6.83 (*t*, *J* = 7.6 Hz, 1H), 6.57 (*t*, *J* = 6.5 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.5, 152.8, 149.3, 136.1, 132.7, 132.3, 132.2, 129.1, 127.9, 125.4, 123.7, 122.6, 122.5, 121.1, 121.1, 120.4, 114.1. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{13}BrN_2O$ $[M+H]^+$: 377.0290, found 377.0280.



105

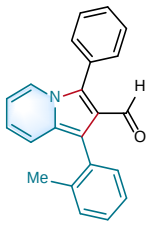
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-phenyl-1-(pyridin-4-yl)indolizine-2-carbaldehyde (**105**, 50.7 mg, 0.17 mmol, isolated yield 85%) as a yellow solid. **mp**: 182−183 ˚C. **FT-IR**: *v* (cm^{-1}): 3050, 2106, 1657, 1628, 1593, 1554, 1533, 1490, 1473, 1436, 1352, 1331, 1300, 1245, 1142, 1119, 1076, 1057, 1006, 950, 863, 824, 769, 756, 723, 711, 696, 686, 668, 635, 622, 612, 546, 499, 443, 414. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.58 (d, *J* = 6.0 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.52 – 7.45 (m, 6H), 7.40 (d, *J* = 6.0 Hz, 2H), 6.76 (dd, *J* = 9.2, 6.4 Hz, 1H),

6.53 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.0, 149.5, 141.6, 132.7, 131.3, 131.1, 129.5, 129.1, 128.1, 125.2, 123.0, 121.9, 121.1, 118.9, 113.7, 111.9. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{14}N_2O$ $[M+H]^+$: 299.1184, found 299.1179.



106

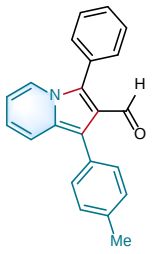
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1,3-diphenylindolizine-2-carbaldehyde (**106**, 50.5 mg, 0.17 mmol, isolated yield 84%) as a yellow solid. **mp**: 164−165 ˚C. **FT-IR**: *v* (cm^{-1}): 3029, 1675, 1591, 1525, 1475, 1442, 1428, 1414, 1383, 1354, 1344, 1331, 1315, 1261, 1236, 1218, 1187, 1146, 1076, 1039, 1022, 989, 948, 925, 905, 843, 822, 804, 750, 740, 729, 711, 692, 674, 633, 604, 585, 569, 511, 488, 435, 414. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.46 – 7.43 (m, 7H), 7.40 – 7.35 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.62 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.43 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.4, 133.1, 131.0, 130.7, 130.6, 130.2, 129.1, 129.0, 128.9, 128.2, 126.8, 122.6, 122.0, 119.6, 119.4, 116.2, 113.5. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{15}NO$ $[M+H]^+$: 298.1232, found 298.1227.



107

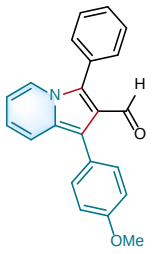
Following the **General procedure D4**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. Work-up gave product 3-phenyl-1-(o-tolyl)indolizine-2-carbaldehyde (**107**, 7.5 mg, 0.02 mmol, isolated yield 12%) as a yellow

solid. **mp**: 68−69 ˚C. **FT-IR**: *v* (cm^{-1}): 3054, 2918, 2850, 1673, 1624, 1599, 1576, 1523, 1447, 1428, 1379, 1356, 1321, 1257, 1166, 1121, 1072, 1018, 969, 921, 903, 797, 750, 732, 692, 618, 571, 540, 503, 484, 445, 404. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.46 – 7.43 (m, 7H), 7.40 – 7.35 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.62 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.43 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.4, 138.1, 131.4, 131.3, 131.0, 130.9, 130.7, 130.0, 129.1, 129.1, 129.0, 128.6, 128.5, 127.6, 125.4, 122.5, 119.9, 118.9, 113.3, 20.2. **ESI-HRMS**: *m/z* calcd. for $C_{22}H_{17}NO$ $[M+H]^+$: 312.1388, found 312.1384.



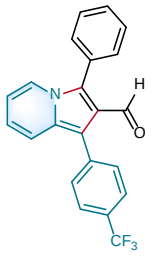
108

Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-phenyl-1-(p-tolyl)indolizine-2-carbaldehyde (**108**, 52.9 mg, 0.17 mmol, isolated yield 87%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3019, 2918, 2848, 2747, 1673, 1626, 1601, 1523, 1504, 1475, 1447, 1428, 1381, 1356, 1323, 1259, 1232, 1183, 1121, 1074, 1041, 1016, 971, 950, 923, 903, 812, 746, 729, 696, 565, 507, 441. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.43-7.42 (m, 4H), 7.38 (d, J = 2.4 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.17 (d, J = 8.0 Hz, 2H), 6.58 (ddd, J = 9.2, 6.4, 1.2 Hz, 1H), 6.42-6.38 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.5, 136.4, 131.2, 130.9, 130.4, 130.0, 129.0, 129.0, 129.0, 128.9, 128.4, 122.5, 122.0, 119.7, 119.2, 116.2, 113.4, 21.2. **ESI-HRMS**: *m/z* calcd. for $C_{22}H_{17}NO$ $[M+H]^+$: 312.1388, found 312.1384.



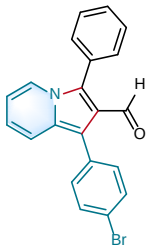
109

Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-(4-methoxyphenyl)-3-phenylindolizine-2-carbaldehyde (**109**, 22.9 mg, 0.07 mmol, isolated yield 35%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3015, 2930, 2833, 2749, 1673, 1605, 1537, 1523, 1504, 1463, 1445, 1428, 1381, 1358, 1286, 1243, 1175, 1109, 1076, 1030, 1020, 948, 923, 903, 833, 785, 748, 729, 696, 666, 565, 528, 488, 439, 410. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.44 (m, 4H), 7.42 – 7.37 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.63 – 6.59 (m, 1H), 6.45 – 6.41 (m, 1H), 3.79 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.6, 158.6, 131.7, 131.0, 130.6, 130.2, 129.0, 129.0, 128.9, 125.3, 122.5, 122.0, 119.7, 119.1, 115.9, 113.7, 113.4, 55.3. **ESI-HRMS**: *m/z* calcd. for $C_{22}H_{17}NO_2$ $[M+H]^+$: 328.1338, found 328.1331.



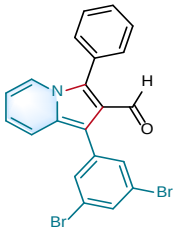
110

Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 3-phenyl-1-(4-(trifluoromethyl)phenyl)indolizine-2-carbaldehyde (**110**, 69.4 mg, 0.19 mmol, isolated yield 97%) as a yellow solid. **mp**: 127−128 ˚C. **FT-IR**: *v* (cm^{-1}): 3058, 2848, 2776, 1669, 1613, 1539, 1523, 1445, 1426, 1409, 1383, 1354, 1317, 1261, 1230, 1160, 1107, 1065, 1016, 939, 903, 843, 833, 756, 736, 703, 692, 674, 600, 558, 490, 455, 439. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.60 (q, J = 8.4 Hz, 4H), 7.52 – 7.45 (m, 5H), 7.40 (d, J = 9.2 Hz, 1H), 6.71 (dd, J = 9.2, 6.4 Hz, 1H), 6.50 (t, J = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.2, 148.6, 137.2 (q, $^4J_{C\text{-}F}$ = 1.2 Hz), 132.2, 131.1, 130.7, 129.4, 129.1, 128.9 (q, $^2J_{C\text{-}F}$ = 32.2 Hz), 128.4, 126.7, 125.0 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 124.4 (q, $^1J_{C\text{-}F}$ = 270.2 Hz), 122.9, 122.0, 120.5, 119.1, 113.6. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -62.3. **ESI-HRMS**: *m/z* calcd. for $C_{22}H_{14}F_3NO$ $[M+H]^+$: 366.1106, found 366.1100.



111

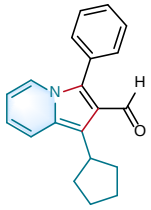
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-(4-bromophenyl)-3-phenylindolizine-2-carbaldehyde (**111**, 67.5 mg, 0.18 mmol, isolated yield 88%) as a yellow solid. **mp**: 150−151 ˚C. **FT-IR**: *v* (cm^{-1}): 3046, 2926, 2846, 2749, 1675, 1597, 1521, 1486, 1447, 1426, 1397, 1379, 1356, 1321, 1259, 1230, 1177, 1123, 1102, 1069, 1039, 1022, 1006, 921, 901, 816, 797, 748, 732, 701, 688, 647, 560, 501, 488, 435, 412. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.50 – 7.45 (m, 7H), 7.38 – 7.32 (m, 3H), 6.69 – 6.65 (m, 1H), 6.47 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.3, 132.1, 131.3, 131.0, 131.0, 130.6, 129.3, 129.1, 128.9, 128.6, 128.2, 122.7, 121.9, 120.8, 120.0, 119.33, 113.5. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{14}BrNO$ $[M+H]^+$: 376.0337, found 376.0335.



112

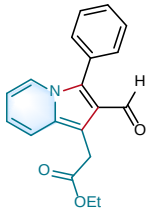
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. Work-up gave product 1-(3,5-dibromophenyl)-3-phenylindolizine-2-carbaldehyde (**112**, 86.1 mg, 0.19 mmol, isolated yield 95%) as a yellow solid. **mp**: 57−58 ˚C. **FT-IR**: *v* (cm^{-1}): 3064, 2844, 2747, 1673, 1578, 1543, 1523, 1475, 1453, 1405, 1377, 1356, 1321, 1300, 1280, 1259, 1232, 1156, 1123, 1105, 1074, 1047, 1026, 989, 956, 925, 907, 851, 750, 740, 694, 672, 641, 618, 577, 523, 488, 422. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 4.4 Hz, 3H), 7.50 – 7.46 (m, 5H), 7.38 (d, *J* = 9.2 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.51 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 187.9, 148.7, 137.8, 137.3, 137.1, 132.1,

131.1, 129.5, 129.1, 128.2, 124.8, 122.9, 122.4, 120.8, 118.9, 113.6, 112.0. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{13}Br_2NO$ $[M+H]^+$: 353.9441, found 353.9442.



113

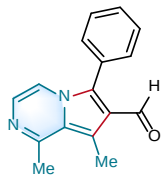
Following the **General procedure D1**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 18 h. work-up gave product 1-cyclopentyl-3-phenylindolizine-2-carbaldehyde (**113**, 26.6 mg, 0.09 mmol, isolated yield 46%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 2949, 2864, 1669, 1599, 1515, 1447, 1428, 1395, 1358, 1315, 1241, 1224, 1164, 1074, 1026, 1001, 973, 927, 886, 744, 725, 696, 554, 495, 439, 406. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.48 – 7.39 (m, 6H), 6.57 – 6.53 (m, 1H), 6.38 – 6.34 (m, 1H), 3.84 – 3.76 (m, 1H), 1.96 – 1.89 (m, 6H), 1.69 – 1.67 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.4, 132.5, 131.2, 129.8, 129.0, 129.0, 129.0, 122.9, 122.6, 120.0, 118.3, 117.5, 112.6, 36.2, 33.3, 26.4. **ESI-HRMS**: *m/z* calcd. for $C_{20}H_{19}NO$ $[M+H]^+$: 290.1547, found 290.1545.



114

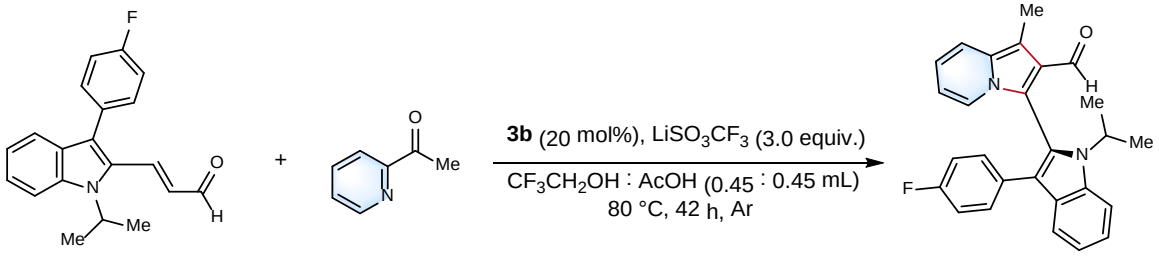
Following the **General procedure D4**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. work-up gave product ethyl 2-(2-formyl-3-phenylindolizin-1-yl)acetate (**114**, 19.6 mg, 0.06 mmol, isolated yield 32%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3056, 2978, 2926, 2835, 2753, 1731, 1665, 1525, 1445, 1389, 1356, 1321, 1249, 1226, 1212, 1175, 1154, 1105, 1076, 1028, 933, 868, 833, 752, 736, 701, 672, 530, 482, 435. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.43 (m, 5H), 7.33 (d, *J* = 9.2 Hz, 1H),

6.67 (ddd, *J* = 9.2, 6.4, 0.8 Hz, 1H), 6.45 – 6.41 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.06 (s, 2H), 1.23 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.3, 171.8, 132.0, 131.6, 131.1, 129.2, 129.1, 128.5, 123.1, 122.7, 119.0, 118.7, 112.9, 105.7, 60.8, 30.1, 14.3. **ESI-HRMS**: *m/z* calcd. for $C_{19}H_{17}NO_3$ $[M+H]^+$: 308.1287, found 308.1281.



115

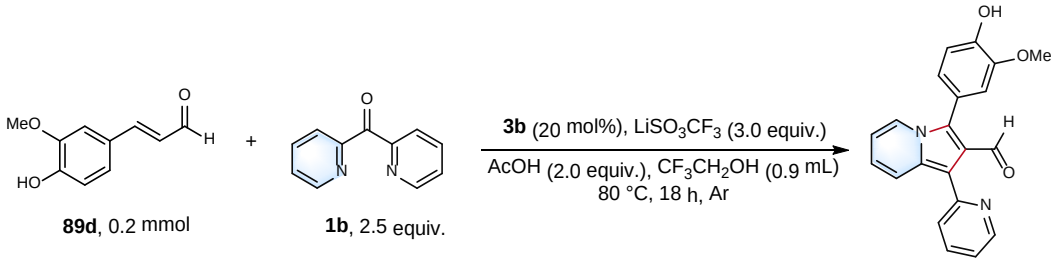
Following the **General procedure D4**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. work-up gave product 1,8-dimethyl-6-phenylpyrrolo[1,2-a]pyrazine-7-carbaldehyde (**115**, 21.5 mg, 0.09 mmol, isolated yield 43%) as a yellow liquid. **FT-IR**: *v* (cm^{-1}): 3060, 2924, 2852, 2737, 1675, 1607, 1502, 1465, 1453, 1432, 1387, 1372, 1352, 1284, 1208, 1152, 1069, 1024, 956, 826, 760, 705, 593, 556, 488. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.51 – 7.45 (m, 4H), 7.39 – 7.37 (m, 2H), 7.21 (d, *J* = 5.2 Hz, 1H), 2.84 (s, 3H), 2.77 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.2, 157.1, 132.7, 130.8, 129.6, 129.2, 127.8, 127.6, 125.7, 123.5, 116.5, 113.7, 24.8, 11.9. **ESI-HRMS**: *m/z* calcd. for $C_{16}H_{14}N_2O$ $[M+H]^+$: 251.1184, found 251.1178.



89p, 0.2 mmol **1a**, 2.5 equiv. **116**, 38%

Preparation of 3-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-1-methylindolizine-2-carbaldehyde (**116**): A mixture of (*E*)-3-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)acrylaldehyde (0.2 mmol), acetylpyridine (2.5 equiv.), catalyst **3b** (0.04 mmol) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH : AcOH (0.45 : 0.45 mL) were stirred at 80 ˚C under Ar atmosphere for 42 h. The reactions were conducted

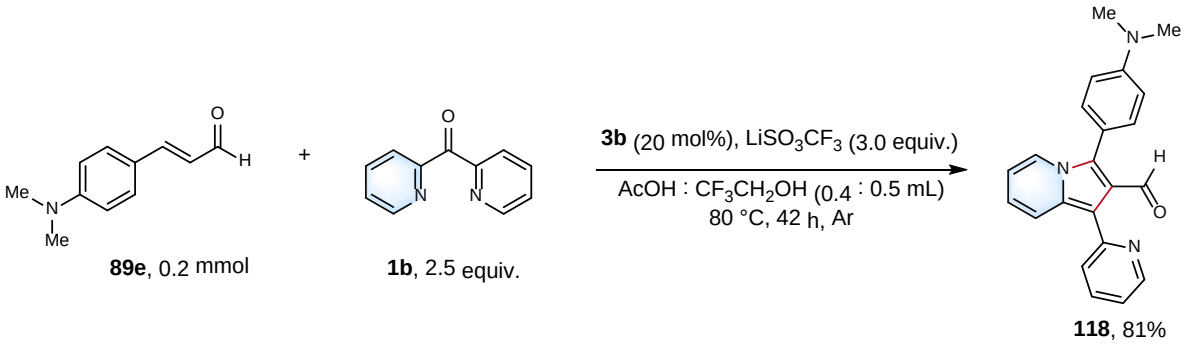
in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by thermometer. After cooling to room temperature, the reaction mixture was basified up to pH 7 *via* stad. Na_2CO_3 aqueous solution, then extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products. Work-up gave product **116** (31.2 mg, 0.08 mmol, isolated yield 38%) as a yellow solid. **mp**: 199−200 ˚C. **FT-IR**: *v* (cm^{-1}): 3039, 2926, 2854, 2743, 2108, 1673, 1599, 1519, 1484, 1475, 1445, 1426, 1395, 1356, 1317, 1259, 1230, 1179, 1123, 1105, 1069, 1039, 1020, 1006, 921, 901, 816, 797, 748, 732, 701, 688, 645, 560, 501, 488, 435, 408. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.05 – 7.01 (m, 2H), 6.82 (t, *J* = 8.5 Hz, 2H), 6.65 – 6.62 (m, 1H), 6.39 (t, *J* = 6.7 Hz, 1H), 4.08 (hept, *J* = 6.9 Hz, 1H), 2.53 (s, 3H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.44 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.6, 161.5 (d, $^1J_{C\text{-}F}$ = 243.9 Hz), 135.8, 131.7, 130.1 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 129.9 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 127.7, 126.2, 123.6, 122.9, 122.7, 120.3, 120.2, 119.7, 119.2, 118.1, 115.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 113.4, 112.4, 110.5, 48.8, 22.0, 21.5, 9.6. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -116.1. **ESI-HRMS**: *m/z* calcd. for $C_{27}H_{23}FN_2O$ $[M+H]^+$: 411.1873, found 411.1854.



89d, 0.2 mmol **1b**, 2.5 equiv. **117**, 79%

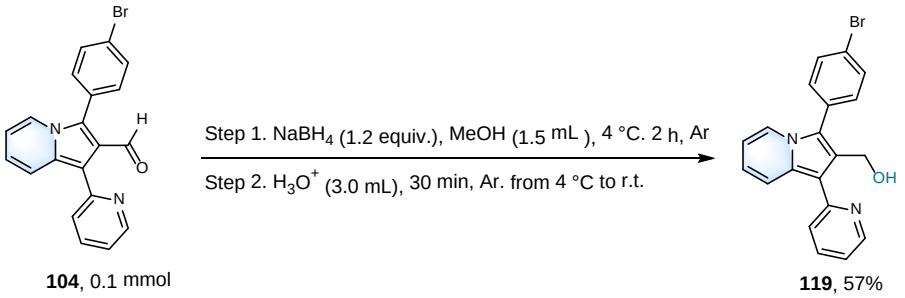
Preparation of 3-(4-hydroxy-3-methoxyphenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**117**): A mixture of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylaldehyde (0.2 mmol), di(pyridin-2-yl)methanone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ˚C under Ar atmosphere for 18 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. 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 *via* stad. Na_2CO_3 aqueous solution, then extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography

on silica gel (ethyl acetate : *n*-hexane) to give products. Work-up gave product **117** (55.0 mg, 0.16 mmol, isolated yield 79 %) as a yellow liquid gel. **FT-IR**: *v* (cm^{-1}): 3017, 2955, 2930, 2848, 2755, 1671, 1587, 1533, 1517, 1475, 1422, 1377, 1346, 1265, 1216, 1168, 1121, 1098, 1057, 1026, 960, 925, 876, 810, 785, 742, 696, 664, 626, 598, 556, 437, 408. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.63 (d, *J* = 4.8 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.15 – 7.11 (m, 1H), 7.00 – 6.93 (m, 3H), 6.76 (dd, *J* = 9.0, 6.7 Hz, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.8, 153.2, 149.1, 147.0, 146.8, 135.9, 132.1, 132.0, 125.6, 124.4, 122.9, 122.2, 121.0, 120.8, 120.4, 120.2, 115.0, 113.7, 113.7, 113.6, 56.1. **ESI-HRMS**: *m/z* calcd. for $C_{21}H_{16}N_2O_3$ $[M+H]^+$: 345.1239, found 345.1234.



Preparation of 3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**118**): A mixture of (*E*)-3-(4-(dimethylamino)phenyl)acrylaldehyde (0.2 mmol), di(pyridin-2-yl)methanone (2.5 equiv.), catalyst **3b** (0.04 mmol), and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH : AcOH (0.5 : 0.4 mL) were stirred at 80 ˚C under Ar atmosphere for 42 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. 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 *via* stad. Na_2CO_3 aqueous solution, then extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products. Work-up gave product **118** (54.6 mg, 0.16 mmol, isolated yield 81%) as a yellow solid. **mp**: 166−167 ˚C. **FT-IR**: *v* (cm^{-1}): 3315, 2899, 2848, 2800, 2774, 2188, 1918, 1665, 1605, 1587, 1535, 1521, 1473, 1440, 1418, 1381, 1354, 1327, 1263, 1228, 1203, 1166, 1117, 1096, 1063, 1053, 1034, 1006, 985, 942, 905, 874, 833, 814, 806, 777, 736, 721, 692, 645, 618, 560, 530, 478, 443, 404. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.59 (d, *J* = 4.8 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.69 – 7.60 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.09 – 7.04 (m, 1H), 6.76 – 6.67 (m, 3H), 6.43 (t, *J* = 6.8 Hz, 1H). **^{13}C**

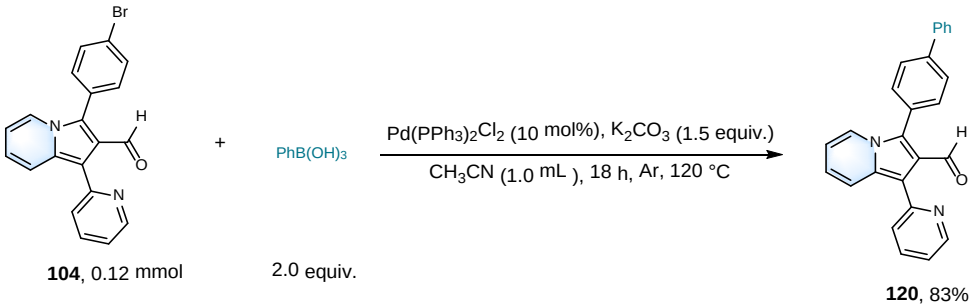
NMR (75 MHz, $CDCl_3$) δ 188.9, 153.5, 150.7, 148.9, 135.6, 133.7, 131.9, 125.5, 122.9, 121.8, 120.7, 120.6, 120.5, 115.1, 113.2, 113.1, 112.0, 40.1. **ESI-HRMS**: *m/z* calcd. for $C_{22}H_{19}N_3O$ $[M+H]^+$: 342.1606, found 342.1603.



104, 0.1 mmol

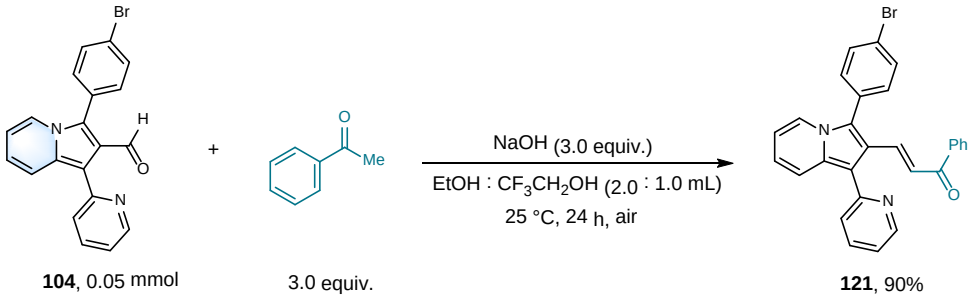
119, 57%

Preparation of (3-(4-bromophenyl)-1-(pyridin-2-yl)indolizin-2-yl)methanol (**119**): A mixture of **104** (0.1 mmol) and $NaBH_4$ (1.2 equiv.) in anhydrous MeOH solution (1.5 mL) were stirred at 4 ºC under Ar atmosphere for 2 h. The reactions were conducted in a sealed Schlenk tube and stirred by an IKA magnetic heating agitator with heating block. The reaction temperature was calibrated by thermometer. After the reaction, the solution was acidified *via* 0.5 N HCl aqueous solution, then stirred for 30 min from 4 ˚C to room temperature. After completion, the solution was extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products. Work-up gave product **119** (22.7 mg, 0.06 mmol, isolated yield 57%) as a yellow solid. **mp**: 99−100 ˚C. **FT-IR**: *v* (cm^{-1}): 2922, 2852, 1587, 1537, 1513, 1473, 1389, 1323, 1273, 1228, 1148, 1123, 1100, 1069, 1055, 1037, 1008, 946, 907, 828, 787, 727, 703, 664, 616, 499, 439, 404. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.4 Hz, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 7.78 – 7.67 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.12 – 7.09 (m, 1H), 6.86 – 6.82 (m, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 4.52 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3, 148.6, 137.4, 132.4, 132.2, 131.5, 129.0, 127.7, 123.5, 123.3, 122.7, 122.5, 120.8, 120.0, 117.6, 111.8, 55.9. **ESI-HRMS**: m/z calcd. for $C_{20}H_{15}N_2OBr$ [M+H]+: 379.0446, found 379.0430.



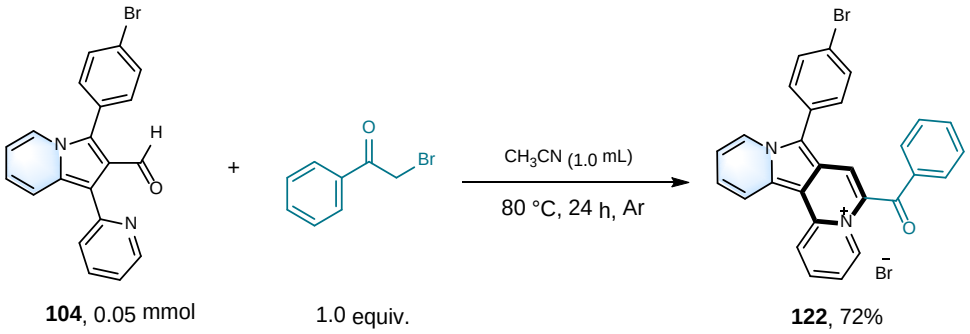
104, 0.12 mmol 2.0 equiv. **120**, 83%

Preparation of 3-([1,1'-biphenyl]-4-yl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (**120**): A mixture of 3-(4-bromophenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (0.12 mmol), phenylboronic acid (2.0 equiv.), catalyst $Pd(PPh_3)_2Cl_2$ (10% mmol), and K_2CO_3 (1.5 equiv.) in the CH_3CN (1.0 mL) were stirred at 120 ˚C under Ar atmosphere for 18 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. 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 *via* stad. Na_2CO_3 aqueous solution, then extracted by diether (3×3 mL) and dried over anhydrous Na_2SO_4. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products. Work-up gave product **33** (37.4 mg, 0.10 mmol, isolated yield 83%) as a yellow solid. **mp**: 146−147 ˚C. **FT-IR**: *v* (cm^{-1}):3058, 3031, 2920, 2854, 2774, 1673, 1630, 1583, 1519, 1475, 1426, 1416, 1356, 1323, 1280, 1269, 1230, 1197, 1181, 1156, 1142, 1100, 1086, 1055, 1034, 1018, 1008, 946, 907, 882, 853, 820, 785, 767, 740, 725, 694, 647, 622, 587, 571, 550, 505, 495, 439, 420, 404. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.64 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.71 – 7.67 (m, 4H), 7.59 (d, J = 7.6 Hz, 2H), 7.55 – 7.46 (m, 3H), 7.41 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 7.2 Hz, 1H), 7.15 – 7.11 (m, 1H), 6.78 (dd, J = 9.6, 6.4 Hz, 1H), 6.53 (t, J = 6.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.7, 153.1, 149.2, 142.0, 140.2, 135.9, 132.3, 131.5, 131.1, 130.3, 128.9, 127.8, 127.7, 127.6, 127.2, 127.1, 125.6, 122.9, 122.4, 121.0, 120.5. **ESI-HRMS**: *m/z* calcd. for $C_{26}H_{18}N_2O$ $[M+H]^+$: 375.1497, found 375.1495.



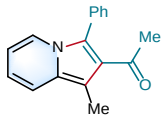
104, 0.05 mmol 3.0 equiv. **121**, 90%

Preparation of (*E*)-3-(3-(4-bromophenyl)-1-(pyridin-2-yl)indolizin-2-yl)-1-phenylprop-2-en-1-one (**121**): A mixture of 3-(4-bromophenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (0.05 mmol), acetophenone (3.0 equiv.) and NaOH (3.0 equiv.) in the EtOH : CF_3CH_2OH (2.0 : 1.0 mL) were stirred at 25 ˚C under air atmosphere for 24 h. The reactions were conducted in a glass tube and stirred by an IKA magnetic heating agitator. The reaction was monitored by TLC. After filtration and concentrated in rotary evaporator, the crude product was purified with flash chromatography on silica gel (ethyl acetate : *n*-hexane) to give products. Workup gave product **121** (21.5 mg, 0.05 mmol, isolated yield 90%) as a yellow solid. **mp**: 173−174 ˚C. **FT-IR**: *v* (cm^{-1}): 3054, 2920, 1655, 1583, 1504, 1471, 1447, 1387, 1341, 1296, 1212, 1177, 1148, 1102, 1072, 1034, 1008, 991, 853, 830, 789, 742, 690, 647, 583, 548, 509, 441, 408. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.4 Hz, 1H), 7.91 (d, *J* = 16.0 Hz, 1H), 7.72 – 7.66 (m, 5H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.34 – 7.32 (m, 4H), 7.17 (d, *J* = 10.0 Hz, 1H), 6.93 (d, *J* = 15.6 Hz, 1H), 6.77 – 6.73 (m, 1H), 6.48 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.9, 154.2, 149.9, 138.2, 137.4, 136.4, 132.9, 132.8, 132.5, 132.3, 129.6, 128.4, 128.2, 125.1, 124.7, 124.1, 123.3, 122.3, 121.0, 120.9, 120.1, 119.0, 114.0, 112.8. **ESI-HRMS**: *m/z* calcd. for $C_{28}H_{19}N_2OBr$ $[M+H]^+$: 479.0759, found 479.07740.



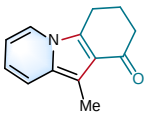
Preparation of 6-benzoyl-8-(4-bromophenyl)indolizino[1,2-a]quinolizin-5-ium bromide (**122**): A mixture of 3-(4-bromophenyl)-1-(pyridin-2-yl)indolizine-2-carbaldehyde (0.05 mmol) and 2-bromo-1-phenylethan-1-one (1.0 equiv.) in the CH_3CN (1.0 mL) were stirred at 80 ˚C under Ar atmosphere for 24 h. The reactions were conducted in a sealed Schlenk tube and heated by an IKA magnetic heating agitator with heating block. The reaction temperature was directly read from temperature detector of IKA apparatus and was calibrated by thermometer. After cooling to room temperature, resulting precipitate was filtered off, washed with *n*-hexane and washed with ethyl acetate, then gave product **122** (20.0 mg, 0.04 mmol, isolated yield 72%) as a red solid. **mp**: 293−295 ˚C. **FT-IR**: *v* (cm^{-1}): 3392, 3060, 1655, 1630, 1597, 1552, 1533, 1492, 1473, 1436, 1354, 1333, 1302, 1245, 1197, 1164, 1142, 1119, 1076, 1057, 1008, 950, 863, 824, 771, 756, 723, 711, 699, 686, 668, 635, 622, 614, 546, 499, 443, 416. **^{1}H NMR** (400 MHz,

DMSO-d_6) δ 9.26 (d, *J* = 8.8 Hz, 1H), 9.19 (d, *J* = 6.8 Hz, 1H), 9.11 (d, *J* = 9.2 Hz, 1H), 8.98 (d, *J* = 6.8 Hz, 1H), 8.49 (t, *J* = 7.8 Hz, 1H), 8.15 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 2H), 7.89 – 7.80 (m, 4H), 7.75 – 7.73 (m, 3H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 6.7 Hz, 1H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 188.9, 142.1, 140.3, 137.7, 135.6, 135.2, 135.2, 132.8, 132.1, 130.8, 130.4, 129.1, 126.3, 126.1, 125.6, 122.9, 122.8, 120.5, 120.1, 119.8, 119.5, 118.7, 118.3, 104.2. **ESI-HRMS**: *m/z* calcd. for $C_{28}H_{18}N_2OBr^+$ [M]: 477.0603, found 477.0596.



123

Following the **General procedure D4**, a mixture of α,β-unsaturated ketone (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. Work-up gave product 1-(1-methyl-3-phenylindolizin-2-yl)ethan-1-one (**123**, 9.5 mg, 0.04 mmol, isolated yield 21%) as a yellow liquid. **mp**: 93−94 ˚C. **FT-IR**: *v* (cm^{-1}): 2922, 1655, 1517, 1469, 1445, 1424, 1350, 1323, 1241, 1168, 954, 859, 767, 738, 701, 670, 647, 589, 554, 495, 422. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 4H), 7.35 – 7.31 (m, 3H), 6.5 – 6.53 (m, 1H), 6.32 (t, *J* = 6.6 Hz, 1H), 2.46 (s, 3H), 1.98 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.3, 131.8, 131.1, 129.9, 129.3, 129.0, 126.1, 126.1, 122.5, 118.7, 116.8, 112.2, 110.1, 31.4, 10.2. **ESI-HRMS**: *m/z* calcd. for $C_{17}H_{15}NO$ $[M+H]^+$: 250.1232, found 250.1227.



124

Following the **General procedure D4**, a mixture of α,β-unsaturated aldehyde (0.2 mmol), heteroaryl ketone (2.5 equiv.), catalyst **3b** (0.04 mmol), AcOH (2.0 equiv.) and $LiSO_3CF_3$ (3.0 equiv.) in the CF_3CH_2OH (0.9 mL) were stirred at 80 ºC under Ar atmosphere for 36 h. Work-up gave product 10-methyl-3,4-dihydropyrido[1,2-a]indol-1(2H)-one (**124**, 15.2 mg, 0.08 mmol, isolated yield 38%) as a yellow solid. **mp**: 111−112 ˚C. **FT-IR**: *v* (cm^{-1}): 2920, 2854, 1649, 1523, 1432, 1414, 1368, 1331, 1265, 1228, 1183, 1140, 1082, 997, 925, 894, 859, 812, 783, 736, 713, 628, 598, 577, 560, 530, 466, 420. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 9.2 Hz, 1H), 6.49 (dd, *J* = 9.0, 6.4 Hz, 1H), 6.44 – 6.41 (m, 1H), 2.85 (t, *J* = 6.2 Hz, 2H), 2.54 – 2.51 (m, 2H), 2.47 (s, 3H), 2.19 (p, *J* = 6.4 Hz,

2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.2, 130.8, 129.9, 121.8, 121.0, 119.1, 116.0, 112.1, 107.8, 39.4, 23.5, 21.1, 9.6. **ESI-HRMS**: *m/z* calcd. for $C_{13}H_{13}NO$ $[M+H]^+$: 200.1075, found 200.1071.

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