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Research progress in natural *N*-glycosides and synthetic methodologies for the formation of *N*-glycosidic bonds

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Abstract

N-glycosides comprise a broad range of compounds, some of which have demonstrated a variety of bioactivities, such as antiviral, antitumor, and antibacterial activities. Serving as essential building blocks for DNA and RNA, nucleosides are a particularly important subclass of *N*-glycosides. Accordingly, natural *N*-glycosides and their analogs have garnered great interests of both organic and pharmaceutical chemists, who have developed numerous synthetic methods for the preparation of *N*-glycosides. By reviewing the natural *N*-glycosides published between 1980 and 2023, this article summarizes current strategies for synthesizing *N*-glycosides, aiming to provide support for the development and research of *N*-glycosides.

Key words: *N*-glycosides; Natural products; Bioactivities; Synthetic methodology; Regioselectivity

1. Introduction

N-glycosides are compounds in which an aglycone is connected to a sugar component through a nitrogen atom.[1] Unlike the numerous *O*-glycosides[2–8] that have been isolated from natural sources, *N*-glycosides are not so common in the nature. To the best of our knowledge, only 30 natural *N*-glycosides have been isolated and characterized between 1980 and 2023. Among them, nucleosides as the essential building blocks of DNA and RNA constitute a special subclass of *N*-glycosides, and their analogs have been developed as drugs that can be used to inhibit viral replication by disrupting DNA/RNA synthesis.[9] Many such modified nucleoside analogs have been used as antiviral drugs for treating HIV, hepatitis B virus, and hepatitis C virus infections[10,11] (Fig. 1). During the COVID-19 pandemic, Merck's molnupiravir was approved by the Food and Drug Administration in December 2021 to contain the spread of COVID-19.[9] Some *N*-glycosides such as gemcitabine,[12] zidovudine,[13] and sinefungin[14] demonstrate antitumor, antibacterial, and antifungal activities in addition to antiviral activities (Fig. 2). Accordingly, *N*-glycosides have attracted great attention from organic and medicinal chemists,[9,15,16] who have developed numerous methods for synthesizing these compounds because of the diverse pharmacological activities. This article summarizes the types and pharmacological activities of *N*-glycosides and the state-of-the-art strategies for the formation of *N*-glycosidic bonds, hoping to provide a solid foundation for further development and research of these compounds.

2. *N*-glycosides isolated from natural sources and their bioactivities

Natural sources such as traditional Chinese medicine still serve as rich reservoirs of novel potential therapeutic agents.[17,18] Tremendous efforts have been made to identify new natural products and map their biological activities for the application in clinical practice. Early in the 1980s, Achari et al and Lee and Han isolated 6 aristolactam *N*-β-D glycosides (**1–6**) from *Aristolochia indica* and *Aristolochia contorta*, respectively.[19,20] A new *N*-glycoside (**7**) was identified from the culture broth of *Actinomadura* sp. SF-2140, which was isolated from a soil sample collected in Hyogo, Japan(Table 1,Fig. 3). In addition, compound **7** was tested for bioactivity and found to be an antiviral agent.[21]

Later, compounds **8** and **9** were isolated from *Bacillus circulans* TB-2125 and found to possess antimicrobial and antimite activities.[22] Subsequently, Kim et al isolated isoguanosine (**10**) with similar structure to adenosine from *Croton tiglium*.[23] In vivo and in vitro pharmacological activity experiments revealed that compound **10** had strong inhibitory effects on tumor cell lines. In 2002 and 2005, Maskey et al isolated 3 indigo-derived *N*-glycoside compounds (**11–13**) from *Streptomyces* GW48/1497.[24,25] Pharmacological experiments showed that compounds **11–13** inhibited various tumor cell lines (CNCL SF268, LCL H460, and MACL; colon cancer cell line CCL HT29; melanoma cell line MEXF 514 L; lung

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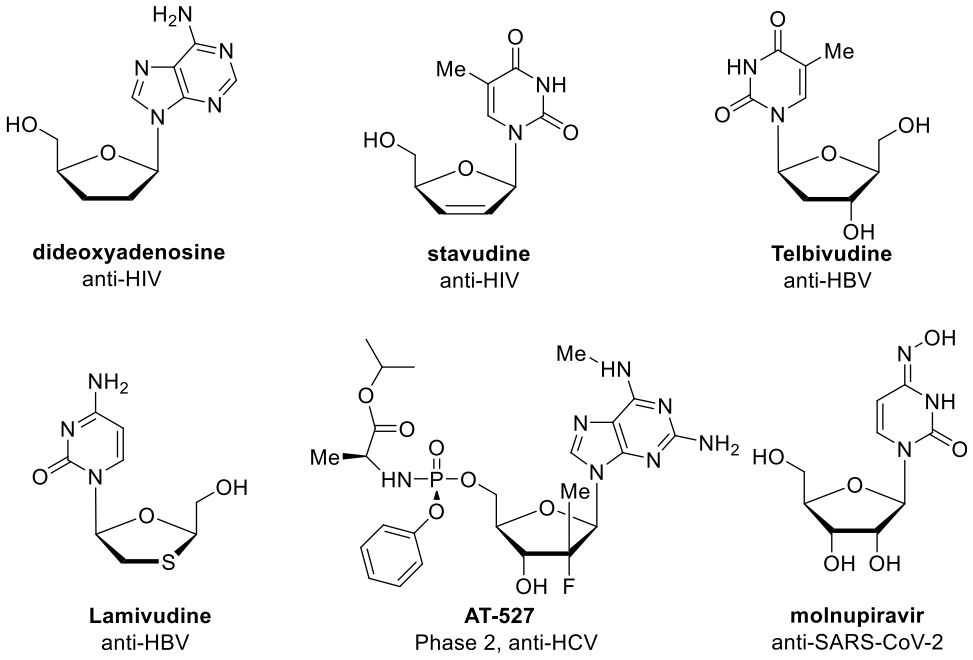


Figure 1. Representative antiviral nucleosides approved by the Food and Drug Administration.

cancer cell lines LXFA 526 L, LXFL, and 529 L; breast cancer cell line MCF-7; and renal cancer cell lines PRCL PC3M, and RXF 631 L). In 2005, Komakine et al team reported a new indole alkaloid *N*-glycoside (**14**) from *Rheum maximowiczii*. Pharmacological experiments showed that compound **14** inhibited the production of I′10 mediated by LPS4.[26] Lu et al and Ma et al isolated 2 novel ansamitocin *N*-glycosides (**15–16**) from *Actinosynnema pretiosum*, in which compound 15 exhibited antitumor activity.[27,28] Teichert et al obtained 4 indole alkaloid *N*-glycosides (**17–20**) from *Cortinarius brunneus*.[29] In 2019, acatechu A (**21**) was isolated from *Areca catechu* by Cao et al, although this compound did not exhibit any toxicity to tumor cells.[30] In 2020, our group isolated 2 new indole alkaloid *N*-glycosides (**22–23**) from *Ginkgo biloba*, and compounds **22** and **23** downregulated the LPS-induced expression of interleukin 6, inducible nitric oxide synthase, and cyclooxygenase-2 at the mRNA level.[31] Zhang et al isolated 6 indole alkaloid *N*-glycosides (**24–29**) from *Aesculus chinensis*. Among them, compounds **24–28** showed moderate neuroprotective activity.[32] Recently, Vu et al isolated a new indole alkaloid *N*-glycoside (**30**) from Vietnamese ginseng.[33] It is noteworthy that compound **30** is an indole propionic acid derivative, whereas most of the previously isolated indole-containing *N*-glycosides are indole acetic acid (IAA) derivatives.

3. Synthetic methodologies for the formation of *N*-glycosidic bonds

The formation of *N*-glycosidic bonds is central to synthesizing *N*-glycosides. The classical route for the synthesis of *N*-glycosides relies on reaction of the aglycon base with a protected sugar possessing a leaving group at the anomeric carbon. Two major problems plague the formation of *N*-glycosidic bonds. One is the difficulty in achieving high yields in *N*-glycosylation and the other in achieving stereochemical control. To address these challenges, tremendous

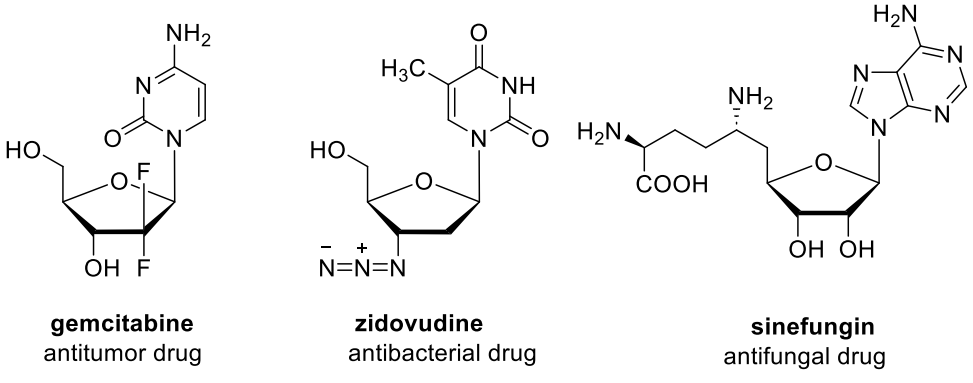


Figure 2. Structures of gemcitabine, zidovudine, and sinefungin.

Table 1

Natural *N*-glycosides and their bioactivities.

Compound no.	Plant sources	Bioactivities	Reference
1	*Aristolochia contorta*	—	[20]
2	*Aristolochia indica*	—	[19]
3	*A indica*	—	[19]
4	*A indica*	—	[19]
5	*A contorta*	—	[20]
6	*A contorta*	—	[20]
7	*Actinomadura* sp. SF-2140	Antibiotic activity	[21]
8	*Bacillus circulans* TB-2125	Antimicrobial and anti-mite activities	[22]
9	*B circulans* TB-2125	Antimicrobial and anti-mite activities	[22]
10	*Croton tiglium*	Antitumor activity	[23]
11	*Streptomyces* GW48/1497	Antitumor activity	[24,25]
12	*Streptomyces* GW48/1497	Antitumor activity	[24,25]
13	*Streptomyces* GW48/1497	Antitumor activity	[25]
14	*Rheum maximowiczii*	Anti-inflammatory activity	[26]
15	*Actinosynnema pretiosum*	Antitumor activity	[27]
16	*A. pretiosum*	—	[27,28]
17	*Cortinarius brunneus*	—	[29]
18	*C brunneus*	—	[29]
19	*C brunneus*	—	[29]
20	*C brunneus*	—	[29]
21	*Areca catechu*	—	[30]
22	*Ginkgo biloba*	Anti-inflammatory activity	[31]
23	*G biloba*	Anti-inflammatory activity	[31]
24	*Aesculus chinensis*	Neuroprotective activity	[32]
25	*A chinensis*	Neuroprotective activity	[32]
26	*A chinensis*	Neuroprotective activity	[32]
27	*A chinensis*	Neuroprotective activity	[32]
28	*A chinensis*	Neuroprotective activity	[32]
29	*A chinensis*	—	[32]
30	Vietnamese ginseng	—	[33]

endeavor has been spent in developing synthetic methods for *N*-glycosidic bond formation with a reasonable yield and good stereoselectivity.[15,16] In general, the methods for the formation of *N*-glycosidic bonds can be classified into 3 categories: Lewis acid–catalyzed C–N bond formation, Pd-catalyzed C–N bond formation, and Au-catalyzed C–N bond formation. The following sections will detail these strategies.

3.1. Lewis acid–catalyzed C–N bond formation

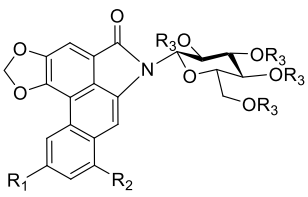
Vorbrüggen glycosylation is a classical, commonly used method for the preparation of pyrimidine, purine, and other heterocyclic nucleosides.[34,35] To achieve better solubility and nucleophilicity, researchers often prepare per-silylated purine or pyrimidine bases by hexamethyl-disilazane or BSA [*N*,*O*-bis-(trimethylsilyl)-acetamide] treatment.[16] The mechanism of Vorbrüggen glycosylation is shown in Fig. 4. A 1′,2′-dioxolenium ion intermediate is generated by intramolecular cyclization of glycosyl acetate **31** in the presence of a Lewis acid. The 1′,2′-dioxolenium ion favors nucleophilic attack from the β-face to give the β-glycosylic product **32**, an example of a neighboring group effect. It is noteworthy that the installation of a 2′-*O*-acyl group is essential for achieving high stereoselectivity due to the participation of this neighboring group in the formation of the 1′,2′-dioxolenium ion. Indeed, α/β-selectivity is poor when 2′-deoxyglycosyl acetate sugars are used in the reaction. Vorbrüggen glycosylations usually require high temperatures and strong Lewis acids and face a challenge for large-scale application. Thus, tremendous efforts have been made to overcome these limitations.[16]

In 2011, Sniady et al developed a Brønsted acid–catalyzed *N*-glycosylation method featuring a 1-flow, multistep synthesis of nucleosides catalyzed by cost-saving and commercially available pyridinium triflates (Fig. 5). This method achieved high-yield production of nucleosides even on a preparative scale.[36] However, the *N*9/*N*7 regioselectivity remained unsatisfactory when a purine substrate **40** was used.

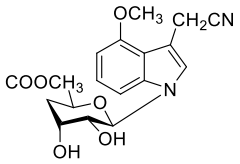
Liao et al reported an effective method for glycosylation of nucleobases by employing glycosyl trifluoroacetimidates **43** as donors under trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis. This *N*-glycosylation protocol requires only a catalytic amount of TMSOTf as a promoter and runs smoothly at room temperature, producing the corresponding nucleosides (**44**, **45**) in moderate to high yields. In this reaction, when the glycosyl donor is protected with an acyl group, 1,2-*trans*-glycosidic bonds are mainly generated. However, when the glycosyl donor is protected with a benzyl group, a mixture of α- and α-anoisomers is generated because there is no *ortho*-group effect (Fig. 6).[37]

In 2013, Mata and Luedtke reported a new *N*-glycosylation method employing a combination of BSA, *N*-iodosuccinimide, and TMSOTf to afford the desired *N*-glycosides. With this new approach, compound **49** could be prepared on a large scale (up to >10 g) via a stereoselective *N*-glycosylation of 2-deoxythioribose (**48**) with 6-bromoquinazoline-2,4-(1*H*,3*H*)-dione (**47**) (Fig. 7).[38]

In 2019, Hu et al developed a new glycosyl donor in the form of EPP [3,5-dimethyl-4-(2′-phenylethynylphenyl)phenyl] glycosides and succeeded in using these EPP glycosides for the *N*-glycosylation of



1. $R_1 = R_2 = R_3 = H$
2. $R_1 = R_3 = H$, $R_2 = OMe$
3. $R_1 = OH$, $R_2 = R_3 = H$
4. $R_1 = OMe$, $R_2 = H$, $R_3 = Ac$
5. $R_1 = R_2 = H$, $R_3 = Ac$
6. $R_1 = OAc$, $R_2 = H$, $R_3 = Ac$



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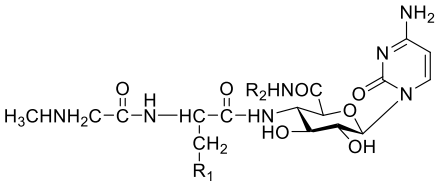
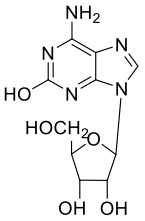


8. $R_1 = NH{-}C(=NH){-}NH_2$ $R_2 = H$
9. $R_1 = NH{-}C(=NH){-}NH_2$ $R_2 = (CH_2)_3NH(CH_2)_4NH_2$



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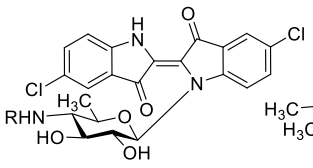
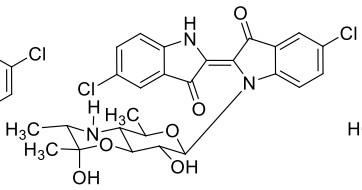


11. R = H
12. R = Ac



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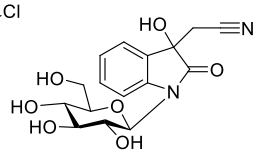

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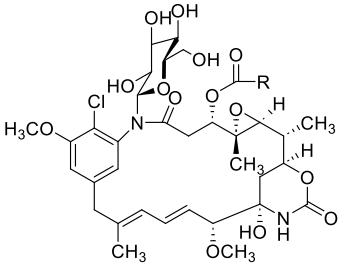
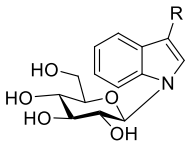
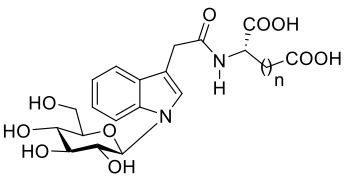


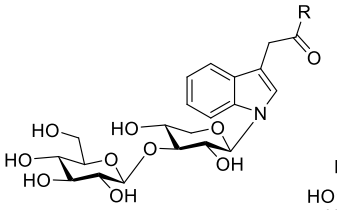
15. R = Et
16. R = Me



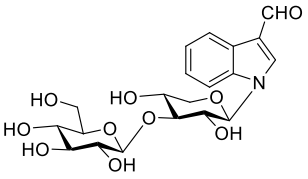
17. $R = CH_2OCH_3$
18. R = CHO
19. $R = CH_2COOH$
20. $R = CH_2COOCH_3$
21. $R = CH_2COOCH_2CH_2CH_2CH_3$



22. n = 2
23. n = 1



24. R = OH
25. $R = OCH_3$



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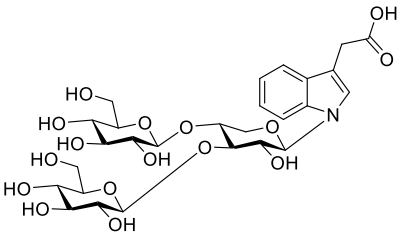

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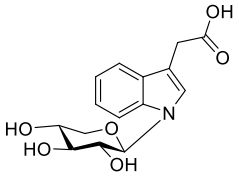

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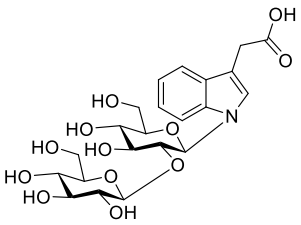

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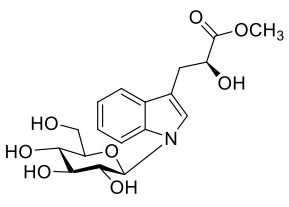

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Figure 3. Chemical structures of isolated *N*-glycosides.

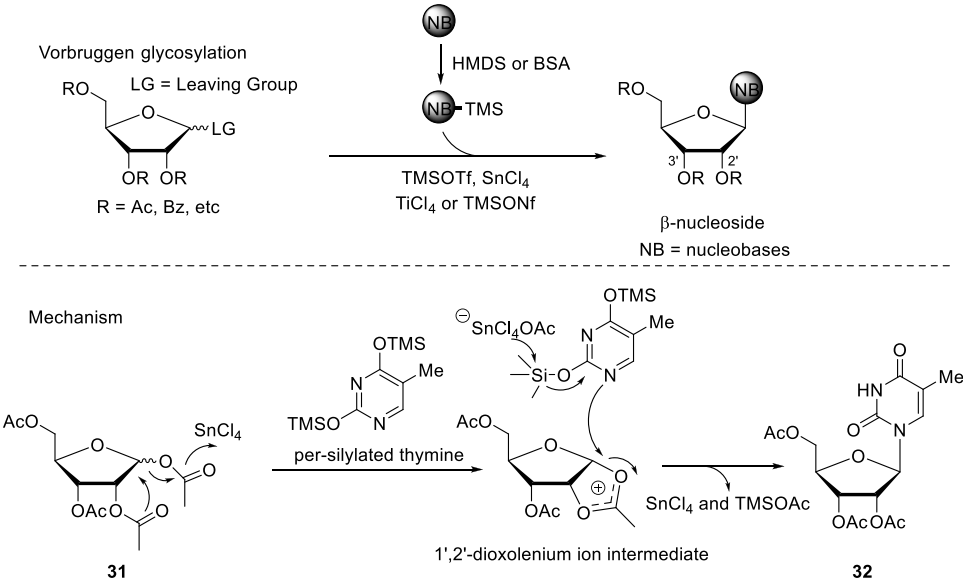


Figure 4. Vorbrüggen glycosylation reaction and its mechanism.

pyrimidine and purine derivatives with an *N*-iodosuccinimide/TMSOTf system (Fig. 8). The glycosylation using purines afforded the desired nucleosides (**53–55**) in good yields (69%–74%). Excellent yields (>90%) were obtained for the glycosylation of pyrimidines after activation and solvation with *N*, *O*-bis (trimethylsilyl) trifluoroacetamide (BSTFA) in CH_3CN.[39]

As mentioned previously, indole-bearing *N*-glycosides are common motifs among natural products and pharmaceuticals and play vital roles in biological processes. To the best of our knowledge, there is still no direct *N*-glycosylation method using indoles due to their poor nucleophilicity. The state-of-the-art methods require initial reduction of indole to indoline (**57**), which may then undergo the glycosylation. The resulting indoline *N*-glycoside (**58**) may then be oxidized to provide the desired indole *N*-glycoside (**59**) (Fig. 9).[31,40]

In 2020, our group isolated 2 *N*-glycosides, *N*-[2-(1-β-D-glucopyranosyl)-1*H*-indol-3-yl)acetyl]-L-glutamic acid (**22**), and *N*-[2-(1-β-D-glucopyranosyl)-1*H*-indol-3-yl)acetyl]-L-aspartic acid (**23**) from *G biloba*. In addition, we devised a concise synthetic route to furnish access to compounds **22** and **23**.[31] As illustrated in Fig. 10, IAA (**56–1**) was treated with ethyl bromide in *N*, *N*-dimethylformamide to give IAA ethyl ester (**56–2**). The reduction of IAA ethyl ester (**56–2**) employing Py·BH_3 (pyridine borane) solution as the reductant furnished 2,3-dihydroIAA-OEt (**57–1**) in 95% yield. 2,3-DihydroIAA-OEt (**57–1**) was subsequently *N*-glycosylated with 1.1 equivalents of D-glucose to yield 2,3-dihydroIAA-OEt-*N*-Glc (**58–1**), which was then oxidized by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to furnish compound **59–1**. Compound **59–1** was hydrolyzed to give IAA-*N*-Glc (**59–2**) and then condensed with L-glutamic acid methyl ester hydrochloride or L-aspartic acid methyl ester hydrochloride, respectively, to give the *N*-glycoside of IAA-amide (**59–3** and **59–4**). Finally, the treatment of the *N*-glucoside of IAA-amide (**59–3** and **59–4**) with 2 M NaOH afforded compounds **22** and **23**.

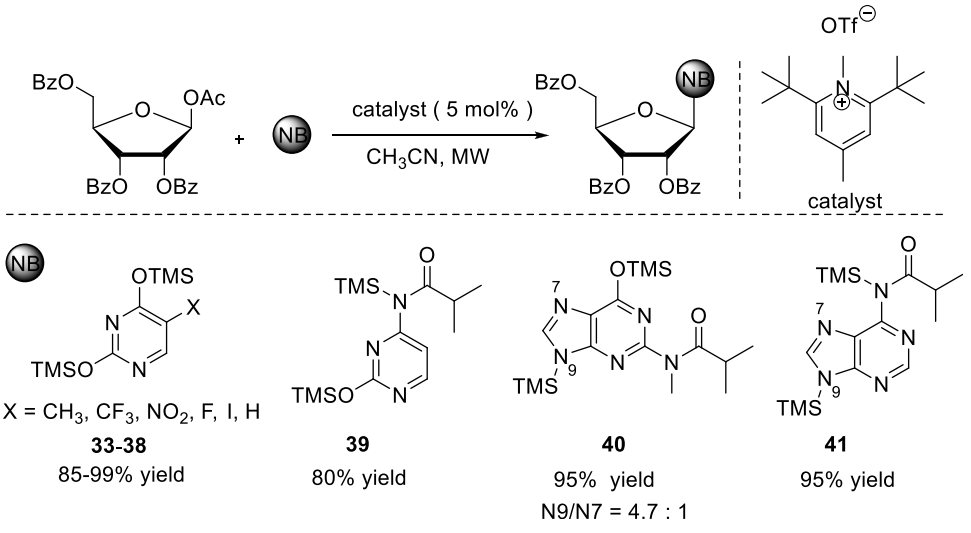


Figure 5. One-flow, multistep synthesis of β-nucleosides by Brønsted acid-catalyzed glycosylation.

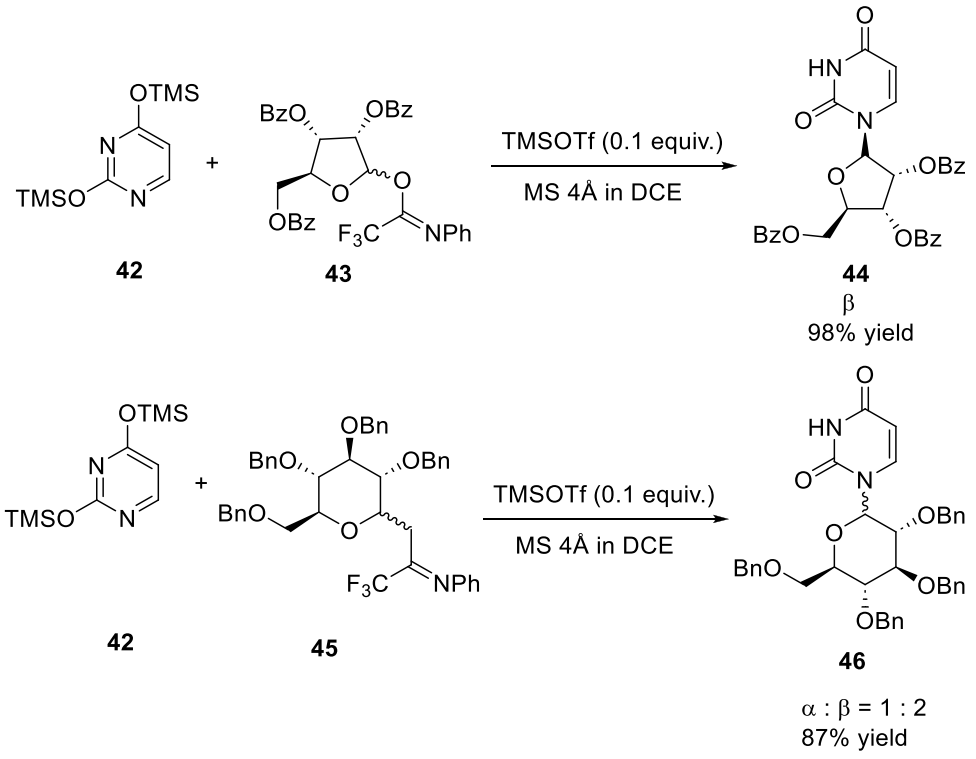


Figure 6. TMSOTf-catalyzed *N*-glycosylation with *N*-phenyl trifluoroacetimide ester as a glycosyl donor. TMSOTf, trimethylsilyl trifluoromethanesulfonate.

3.2. Pd-catalyzed C–N bond formation

In 1992, Bolitt et al developed a palladium(0)-catalyzed synthetic approach for the production of 2′,3′-unsaturated nucleoside analogs. Such nucleosides were previously prepared from acylated glycals with heterocyclic bases under acid catalysis. This strategy, however, often produced mixtures of 2′,3′-unsaturated anomers and 1′,2′-unsaturated anomers. In contrast, the palladium(0)-mediated coupling reaction method developed by Bolitt et al proceeded with excellent regioselectivity and remarkable retention of configuration. However, in some cases, a small amount of β-isomer was generated (Fig. 11).[41]

In 2006, Guppi et al realized a highly stereoselective palladium-catalyzed *N*-glycosylation reaction. In this system, benzimidazole (**65**) and a Boc-protected pyranone (**66, 68**) were coupled to furnish L-2-deoxy-β-ribo-hexopyranosyl nucleosides (**67, 69**) in a highly enantioselective and diastereoselective manner with complete retention of configuration. This strategy has the potential to produce natural and unnatural nucleoside analogs (Fig. 12).[42]

In 2015, Ji et al reported a novel approach for synthesizing diverse *N*-heterocyclic glycosides. Various *N*-nucleophiles were successfully transformed into the corresponding *N*-glycosides in good to excellent yields with β- or α-selectivity based on palladium-catalyzed allylation. Glycosylated indirubins, potent inhibitors of kinases, were prepared with this methodology (Fig. 13).[43]

In 2018, Dai et al reported a stereoselective decarboxylation reaction between 3,4-*O*-carbonate glycal (**75–79**) and *N*-tosyl functionalized aliphatic and aromatic amines via palladium-catalyzed decarboxylative allylation (Fig. 14). A wide range of highly functionalized 2,3-unsaturated-β-*N*-glycosides (**80–84**) were furnished in good to excellent yields and exquisite regioselectivities and stereoselectivities (β:α > 30:1). A plausible mechanism for this reaction is shown in Fig. 14. The Pd(0) complex, generated from reduction of Pd(II) acetate and subsequently complexed with the ligand, coordinates to the double bond of glycal from less sterically demanding α-face to form intermediate **A**. Next, a η3-π-allyl-Pd(II) moiety **B**

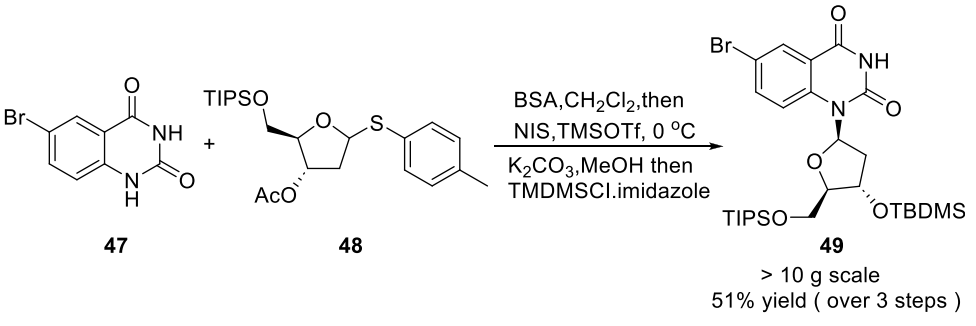


Figure 7. A new *N*-glycosylation method developed by the Luedtke group.

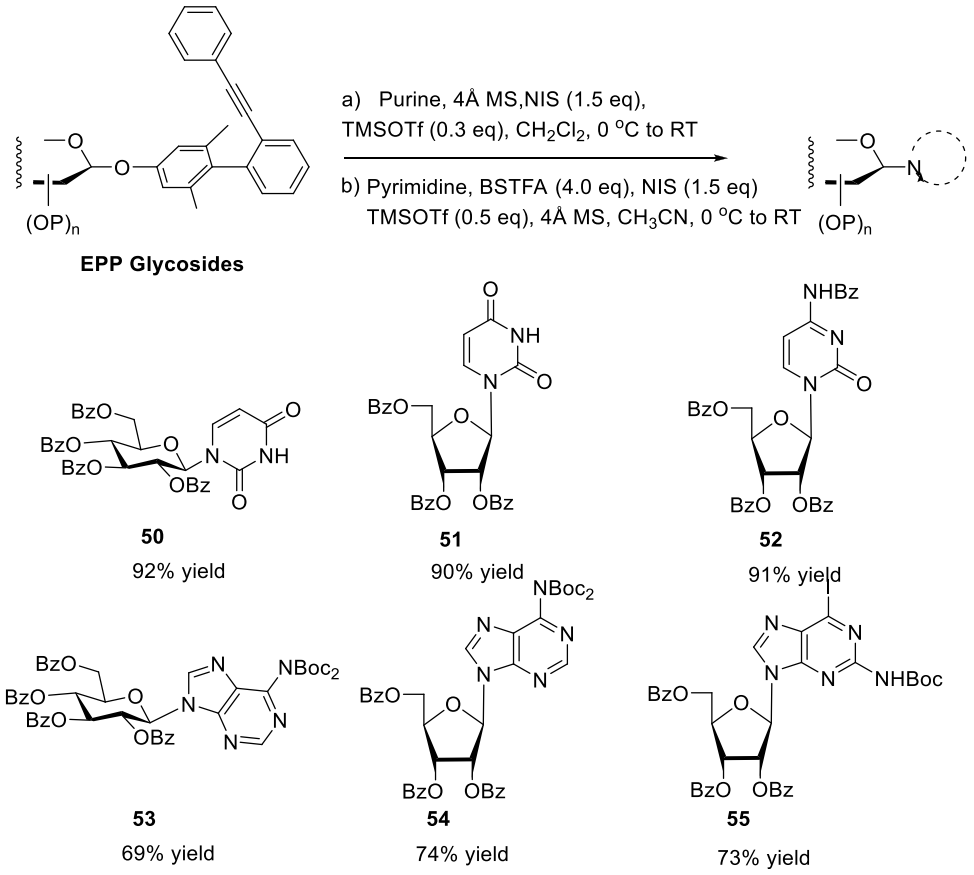


Figure 8. EPP glycoside-mediated *N*-glycosylation developed by Yu's group. EPP, 3,5-dimethyl-4-(2′-phenylethynylphenyl)phenyl.

is produced from an oxidative addition process, during which the carbonate group is omitted. Subsequently, the final product **D** is generated from nucleophilic addition by nucleophile sulfonamides with the retention of stereochemistry.[44]

3.3. Au-catalyzed C–N bond formation

For substrates such as purines, it is often difficult to achieve high yields and high *N9*/*N7* regioselectivities in C–N bond–forming reactions. In 2011, Zhang et al made a breakthrough by developing an ester-type glycosyl donor (**85**), which could facilitate Au-catalyzed *N*-glycosylations between glycosyl *ortho*-hexynylbenzoates (**85**) and nucleobases (Fig. 15). This protocol allowed efficient and regioselective *N9*-glycosylations of purines under mild conditions.[45]

2′-Deoxy-β-D-ribonucleosides and their oligomers constitute the important biopolymer DNA and play a vital role in a variety of genetic processes. In addition, anticancer and antiviral drugs, such as cladribine and floxuridine, also bear 2′-deoxy-β-D-ribonucleoside motifs as core structural features. The absence of a directing group at the C2′ position poses a challenge to their synthesis. In 2012, Yang et al developed an approach of $Ph_3PAuNTf_2$-promoted stereoselective *N*-

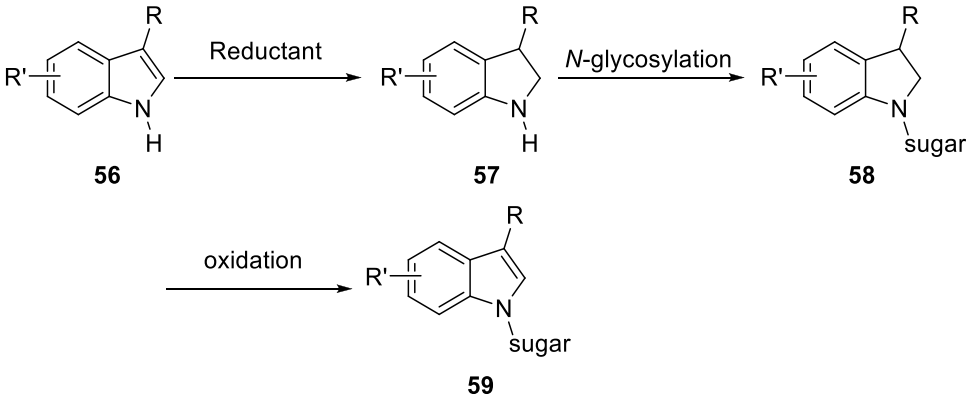


Figure 9. Current strategy for the *N*-glycosylation of indole substrates.

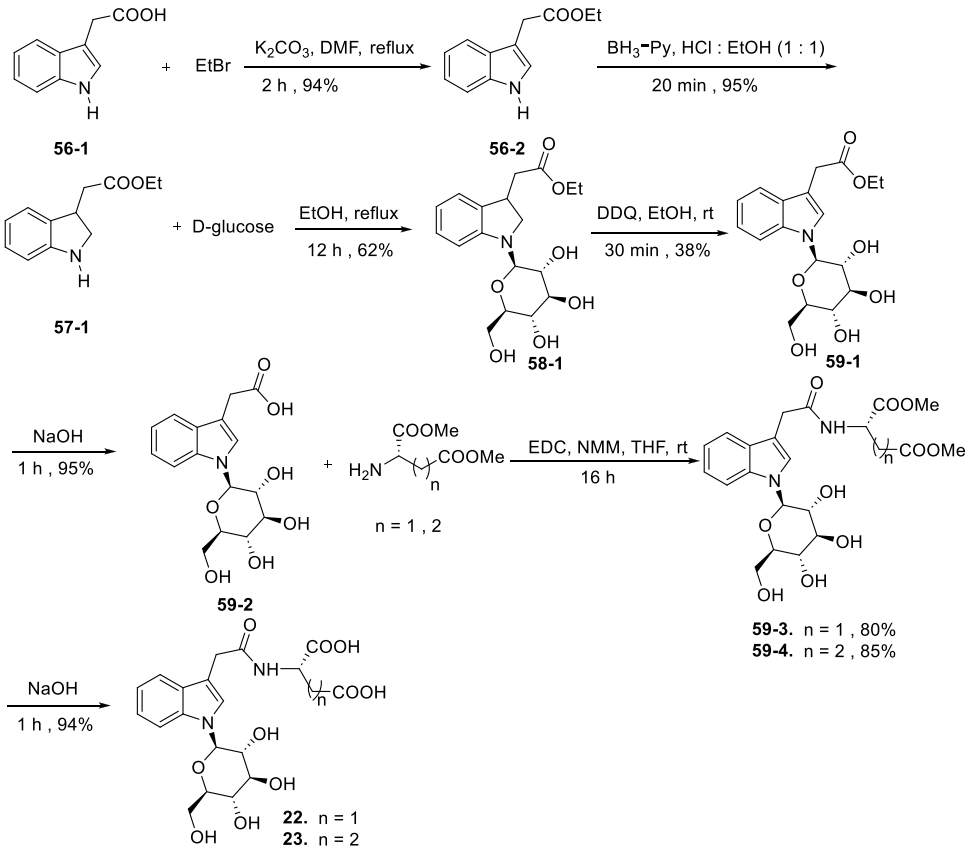


Figure 10. A concise synthetic route for compounds **22** and **23**.

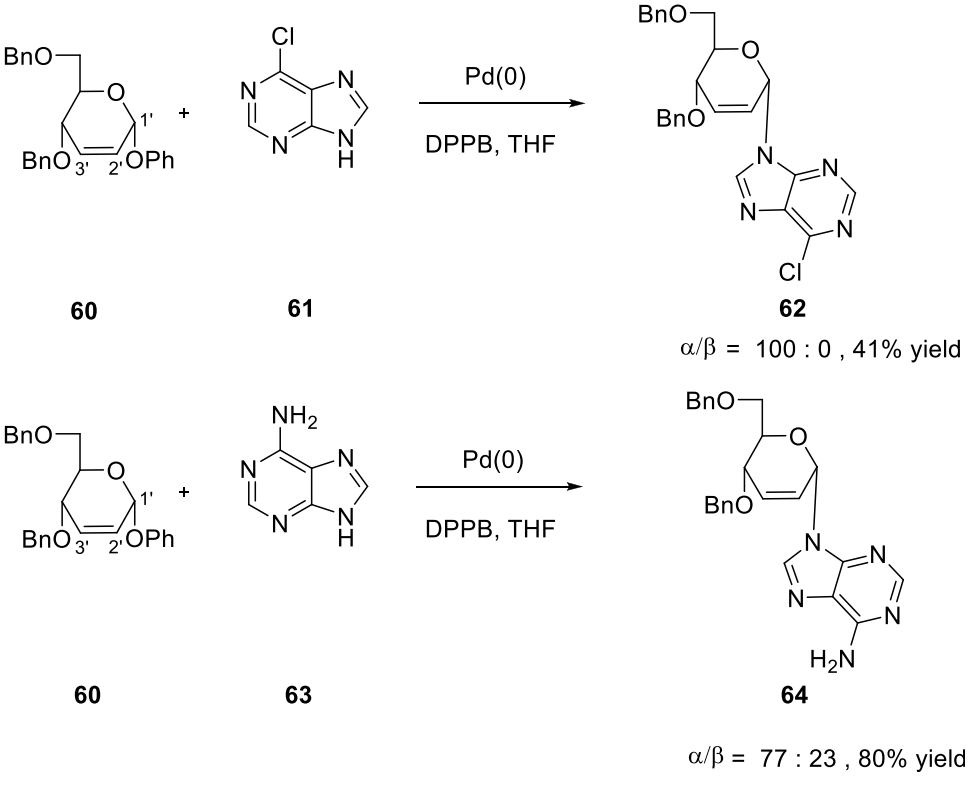


Figure 11. Palladium(0)-catalyzed *N*-glycosylation.

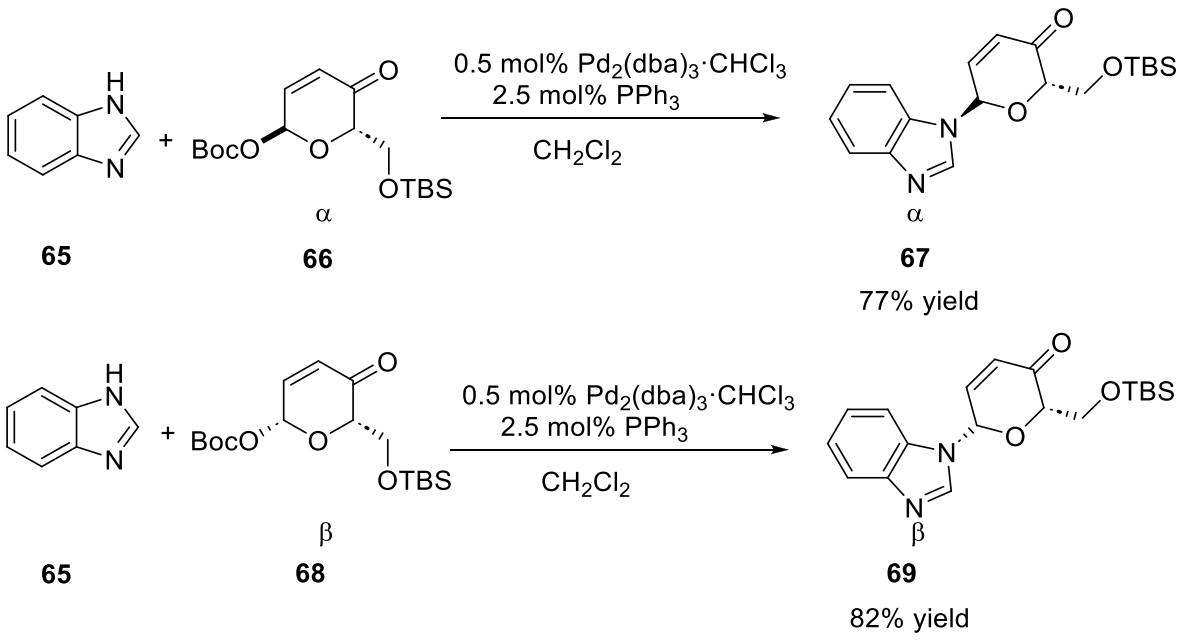


Figure 12. Palladium-catalyzed synthesis of L-2-deoxy-β-ribo-hexopyranosyl nucleosides.

glycosylation for the synthesis of 2′-deoxy-β-D-ribonucleosides (**92**) (Fig. 16). Concentration had a strong effect on the stereoselectivity of the *N*-glycosylation.[46]

In 2022, using glycosyl (*Z*)-ynenoates (**93**) as donors, Liu et al developed a highly efficient gold(I)-catalyzed *N*-glycosylation approach for the versatile synthesis of various types of nucleosides and deoxynucleosides, affording 31 pyrimidine nucleosides and 8 purine nucleosides in high yields (Fig. 17). In particular, this approach addressed the challenge of *N9*/*N7* regioselectivity associated with the purine substrate and achieved the synthesis of a variety of drugs including floxuridine, trifluridine, decitabine, and cladribine.[47]

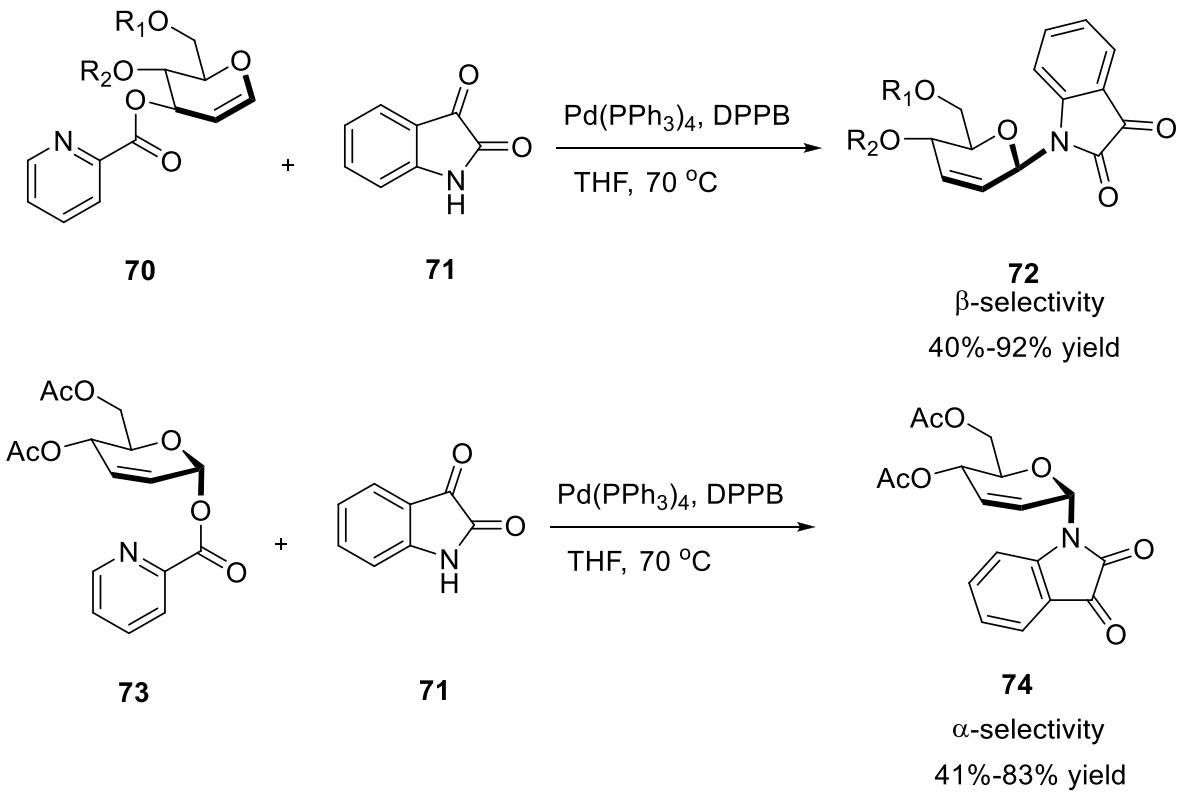


Figure 13. Palladium-catalyzed *N*-glycosylation developed by Liu's group.

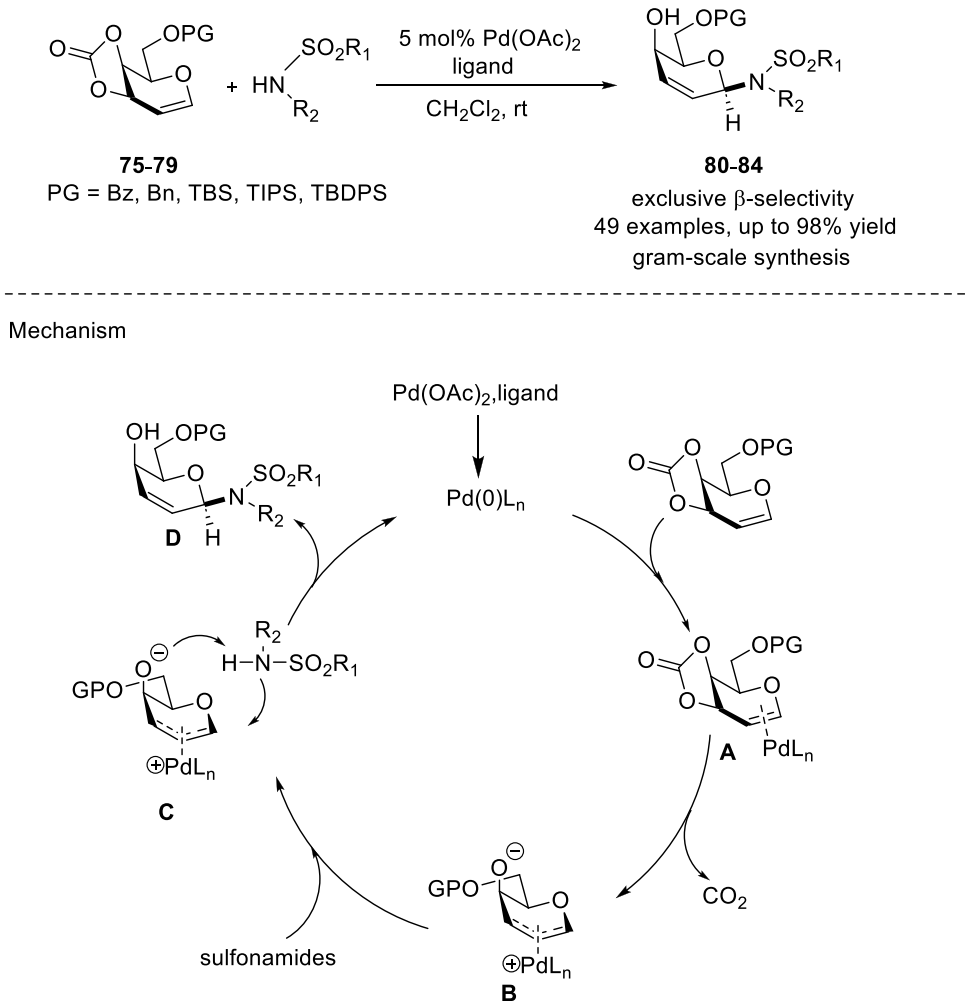


Figure 14. *N*-glycosylation route and mechanism for the synthesis of 2,3-unsaturated-β-*N*-glycosides under Pd catalysis.

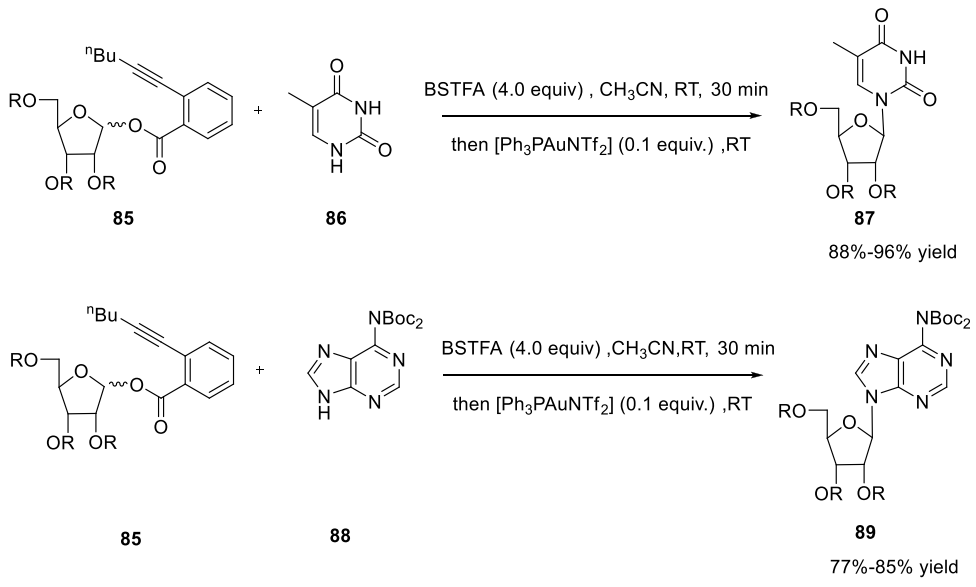
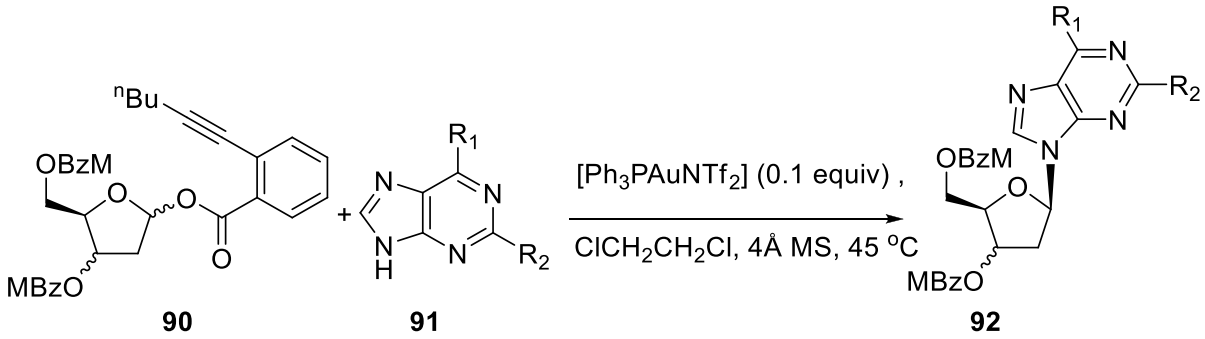


Figure 15. Au-catalyzed *N*-glycosylation between glycosyl *ortho*-hexynylbenzoates and nucleobases.



entry	purine	Conc. (mM)	β/α ratio	yield (%)
1	**91a** (R_1=I, R_2=NHBoc)	25	2.8 : 1	100
2	**91a** (R_1=I, R_2=NHBoc)	10	4.2 : 1	100
3	**91a** (R_1=I, R_2=NHBoc)	2.5	9.7 : 1	97
4	**91a** (R_1=I, R_2=NHBoc)	1.0	15 : 1	89

Figure 16. Stereoselective *N*-glycosylation for the synthesis of 2′-deoxy-β-D-ribonucleosides.

4. Conclusions

N-glycosides and their analogs demonstrate great potential for treating viral diseases and cancers. This review summarized the types and activities of *N*-glycosides isolated from natural sources and introduced different synthetic methodologies for glycosidic C–N bond formation. Although great progress has been achieved in the synthesis of *N*-glycosides, there remain opportunities for reaction improvements, such as maximizing yields and stereoselectivities, particularly in reactions to be implemented on a large scale. With further advances in synthetic biology, these synthetic problems may be eventually overcome by mining of efficient and specialized enzyme

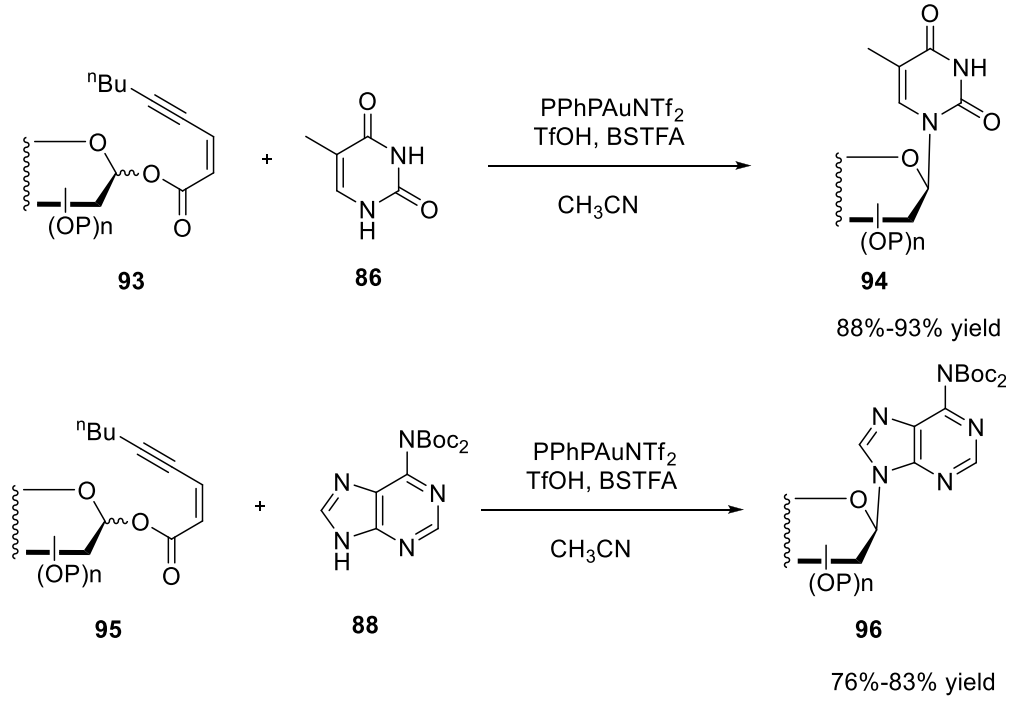


Figure 17. Gold(I)- catalyzed *N*-glycosylation with glycosyl (*Z*)-ynenoates as donors.

catalysts. We hope that this review will serve as a useful aid to medicinal chemists seeking inspiration from natural *N*-glycosides and allow them to develop more efficient and stereoselective methods to synthesize chemical agents for combating illnesses such as AIDS and cancers.

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Statement of ethics

Not applicable.

Conflict of interest statement

No conflict of interest has been declared by the authors.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Author contributions

Yingting Xia and Jintang Cheng drafted the manuscript. Wenjun Wang, Lidong Shao, Guodong Li and An Liu helped generate the figures. Alastair N. Herron, Guodong Li, An Liu and Jintang Cheng contributed to the concept and design and critically edited the manuscript. All authors read and approved the final manuscript.

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