Stereoselective Synthesis of 2-Deoxy-α-N-Glycosides from Glycals with 1,4,2-Dioxazol-5-ones

Zhenpeng Shen¹, Guoyin Yin¹, and Yangyang Li¹

¹Wuhan University

May 06, 2024

Abstract

The synthesis of N-glycosides has received significant attention due to their crucial role in carbohydrate chemistry. Despite considerable advancements were developed in the construction of N-glycosides, methods for the stereoselective construction of 2-deoxy-α-N-glycosides are still limited. Herein, we disclosed a nickel-catalyzed hydroamination of glycals under mild conditions. This transformation could allow for the stereoselective synthesis of an array of 2-deoxy-α-N-glycosides with excellent α-stereoselectivity. Nickel-catalyzed glycosylation reactions, particularly those involving anomeric C(sp3)-metal bond formation, have proven to be an effective and stereoselective strategy for producing various N-glycosides. Additionally, with highlight the application of this reaction, γ-sugar amino acid derivatives were synthesized by one step.

Cite this paper: Chin. J. Chem. 2024, 42, XXX—XXX. DOI: 10.1002/cjoc.202400XXX

Stereoselective Synthesis of 2-Deoxy-α-N-Glycosides from Glycals with 1,4,2-Dioxazol-5-ones

Zhenpeng Shen, Guoyin Yin*, and Yangyang Li*

The Institute for Advanced Studies, Wuhan University, Wuhan 430072, China

Keywords

2-Deoxy-α-N-Glycosides | Nickel catalysis | Stereoselectivity | Glycals | Hydroamination |

Comprehensive Summary

The synthesis of N-glycosides has received significant attention due to their crucial role in carbohydrate chemistry. Despite considerable advancements were developed in the construction of N-glycosides, methods for the stereoselective construction of 2-deoxy-α-N-glycosides are still limited. Herein, we disclosed a nickel-catalyzed hydroamination of glycals under mild conditions. This transformation could allow for the stereoselective synthesis of an array of 2-deoxy-α-N-glycosides with excellent α-stereoselectivity. Nickel-catalyzed glycosylation reactions, particularly those involving anomeric C(sp3)-metal bond formation, have proven to be an effective and stereoselective strategy for producing various N-glycosides. Additionally, with highlight the application of this reaction, γ-sugar amino acid derivatives were synthesized by one step.

Background and Originality Content

Carbohydrates play a crucial role in a myriad of biological processes and have emerged as key compounds in living systems and medical science. [1] N -glycosides, a prominent class of carbohydrates, are extensively found in a wide array of pharmaceuticals, bioactive compounds, and natural products. [2] They also play essential roles in numerous physiological and pathological processes. [3] Although β -glycosylamino anomers are commonly encountered, a significant number of natural glycoproteins are characterized by α -linkage at the anomeric center of their peptide motifs (Fig. 1a) [3; 4]. An exemplary case in point is trehalozolin [5], a trehalase inhibitor. Additionally, the diverse functional implications of these carbohydrate derivatives are further illustrated by compounds such as N -mannosyl tryptophan. [6] This compound is a key agent in posttranslational protein modifications. Another example is Nephritogenoside [4b, c, 7], a glycopeptide from the glomerular basement membrane of rats, noted for its role in inducing glomerulonephritis.

Figure 1. Stereoselective Synthesis of 2-deoxy-α-N-glycosides.
The modification of asparagine residues through 2-deoxyglycosylation has been shown to enhance the hydrolysis-resistant stability of peptide chains, thereby increasing both biological activity and selectivity. As a result, the N-(2-deoxyglycosyl)-amide motif holds significant value in the fields of biochemistry and pharmacology.\[^8\] Despite its significance, literature on synthetic methodologies for this structure remains sparse.\[^9\] Among the known synthetic strategies, the direct N-(2-deoxyglycosyl)-amide formation from nucleophiles and glycals stands out as a notably straightforward approach for generating 2-deoxysugar compounds. Particularly for the synthesis of sulfonamide and simple amide groups with the employment of various transition-metal catalysts, organocatalysts, and Brønsted acid catalysts.\[^10\] These methods predominantly facilitate the production of thermodynamically favored β-amid glycosyl amides.\[^10b, 11\] However, the selective synthesis of thermodynamically disfavored α-glycosyl amides, especially 2-Deoxy-α-N-glycosides, remains a formidable task.\[^8d\]

Transition-metal-catalyzed glycosylation reactions have emerged as highly efficient tools for synthesizing a wide range of glycosides and glycoconjugates. However, when it comes to the synthesis of α-N-glycosides, methods utilizing transition-metal catalysis are currently limited.\[^12\] Considering the significance of α-N-glycosides in medicinal chemistry, there is a strong need to develop an efficient method for their assembly. In this context, the crucial factor in achieving this transformation lies in the discovery of appropriate amidating reagents. In recent studies, Seo and Chang, Yu, and Zhu\[^13\] have identified 1,4,2-dioxazol-5-ones as effective electrophilic amidating reagents in Ni-catalyzed hydroamination reactions. Building upon this knowledge, we propose the extension of Ni-catalyzed hydrofunctionalization to the hydroamidation of glycals with dioxazolones. This strategy would enable the direct synthesis of a diverse array of 2-deoxy-α-N-glycosides. As depicted in Figure 1c, we proposed a plausible mechanism: the reaction initiates with the syn-addition of azolones. This strategy would enable the direct synthesis of a diverse array of 2-deoxy-α-N-glycosides. Notably, this reaction demonstrates a broad substrate scope and remarkable tolerance towards diverse functional groups. Furthermore, we have extensively explored the synthetic applicability of this method through gram-scale experiments.

### Results and Discussion

#### Table 1. Reaction Development of Ni-Catalyzed Hydroamination from Glycals with Dioxazolones

| Reaction conditions: NiBr₂-DME (5 mol%), L (5 mol%), NaI (30 mol%), (MeO)₃SiH (0.8 mmol, 4.0 equiv), 1a (0.2 mmol, 1.0 equiv), 2a (0.4 mmol, 2.0 equiv), 1,4-Dioxane:THF (4:1, 0.27M), t-BuOH (0.6 mmol, 3.0 equiv), 20 °C, 24 h. \[b\] yield of 3a were determined by ¹⁹F NMR with 1-chloro-4-fluorobenzene as an internal standard. \[c\] Yield of isolated product. |

#### Table 2 Substrate Scope of Ni-Catalyzed Hydroamination from Glycals with Dioxazolones

| Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2 (0.4 mmol, 2.0 equiv), NiBr₂-DME (5 mol%), L (5 mol%), NaI (30 mol%), (MeO)₃SiH (0.8 mmol, 4.0 equiv), 1,4-dioxane:THF (4:1, 0.27M), t-BuOH (0.6 mmol, 3.0 equiv), 20 °C, 24 h. |

Our initial investigations focused on the α-selective N-glycosylation of tri-O-benzyl-D-glucal (1a) using 3-(4-fluorophenyl)-1,4,2-dioxazol-5-one (2a) as the amidating reagent. We discovered that NiBr₂[?][DME], combined with the chiral pyridoxaline ligand (L4) and trimethoxysilane, delivered the desired hydroamination product 3a in an isolated yield of 82% with exceptional α-selectivity (entry 1). Subsequently, we explored the impact of ligand steric hindrance on the reaction’s yield. By increasing the steric hindrance of the ligands (L2-L4) through modifications in the substituents on the pyridine, we observed significantly improved yields. However, other ligands (L5-L6) resulted in notably lower yields (entries 2-6). Furthermore, when using alternative nickel sources such as NiCl₂[DME], lower yields were obtained (entry 7). Dimethoxy(methyl) silane and di-ethoxy(methyl) silane were found to be less effective (entries 8-9). The ad-

---

\[^8\] This is a preprint and has not been peer-reviewed. Data may be preliminary.
dition of other proton sources, such as H$_2$O and CH$_3$OH, showed improvements in yield. However, t-BuOH proved to be optimal (entries 10-12). Of note, the inclusion of a catalytic amount of NaI as an additive was crucial for the reaction (entry 13), although the exact role of NaI is still being investigated.

With the optimized reaction conditions in hand, we proceeded to investigate the substrate scope of this reaction, and the summarized results can be found in Scheme 2. Initially, phenyl dioxazolones with mono- and di-substituted groups were examined. It was observed that phenyl dioxazolones substituted with electron-withdrawing groups smoothly underwent the reaction, resulting in the formation of the desired products (3a-3d) with good yields and excellent $\alpha$-selectivity. The absolute $\alpha$-anomeric configuration of the products was confirmed through X-ray crystal structures of 3a and 3d. Unsubstituted phenyl dioxazolones (3e) provided the target product with good yields and excellent $\alpha$-selectivity, while phenyl dioxazolones with electron-donating substituents such as methyl (3f), methoxy (3g), and phenoxy (3h) were also investigated, demonstrating high yields and stereoselectivity. Furthermore, phenyl dioxazolones with di-substituted groups were converted to their $N$-(2-deoxyglycosyl)-amide counterparts (3i and 3j) in moderate yields. Moreover, dioxazolones with fused-ring systems also yielded the target products (3k and 3l) in excellent yields. To further strengthen the synthetic utility of this method, the $N$-(2-deoxyglycosyl)-amides were also successfully prepared from dioxazolones derived from probenecid (3m). However, alkyl dioxazolones were found to be incompatible with this transformation. The hydroamination reaction proceeded smoothly for a diverse range of glycals with various functional groups, as demonstrated in Table 2. Most of the glycals derived from D-glucal reacted smoothly with 3-(4-fluorophenyl)-1,4,2-dioxazol-5-one (2a) under standard conditions yielding good to high results with excellent $\alpha$-stereoselectivity (3o-3r). Notably, high yields and good stereoselectivity were also obtained with the unprotected primary alcohol group on the glycals (3p). Furthermore, the reaction was also successful with glycals derived from galactal. When using these substrates, the reaction proceeded smoothly, resulting in moderate yields and excellent stereoselectivity (3s-3v).

To demonstrate the practical application of this protocol, a gram-scale reaction was conducted, resulting in the synthesis of the desired product 3a with moderate yield and excellent selectivity, as depicted in Figure 2a. Moreover, we extended the utility of this methodology for the synthesis of 2-deoxy sugar amino acids (SAAs), as illustrated in Figure 2b. Initially, readily available glycals were subjected to oxidation and methylation, yielding 6-carboxy glycals (4). By employing our developed method, the target compound, 1-amino-2-deoxy-$\alpha$-D-galacturonic acid derivative (5), was obtained directly in a single step with moderate yield and high stereoselectivity. Sugar amino acids represent highly substituted polyfunctional building blocks that hold significant potential in drug discovery and materials science.

**Figure 2**. Gram-Scale reaction and synthetic application.

Gram-scale reaction conditions: NiBr$_2$·DME (5 mol%), L (5 mol%), NaI (30 mol%), (MeO)$_3$SiH (12 mmol, 4.0 equiv), 1 (3 mmol, 1.0 equiv), 2 (6 mmol, 2.0 equiv), 1,4-dioxane:THF (4:1, 0.27 M), t-BuOH (9 mmol, 3.0 equiv), 20 °C, 24 h.

**Conclusions**

In conclusion, we have successfully developed a nickel-catalyzed hydroamination reaction for the stereoselective synthesis of 2-deoxy-$\alpha$-N-glycosides from glycals and 1,4,2-dioxazol-5-ones. Notably, the reaction proceeds under mild conditions, exhibits a broad substrate scope, excellent $\alpha$-stereoselectivity, and remarkable tolerance towards diverse functional groups. Furthermore, we have exemplified the versatility of this reaction through the one-pot, stereoselective synthesis of 2-deoxy sugar amino acids, which hold significant promise in applications in drug discovery and materials science.

**Experimental**

**General Procedure for the Ni-Catalyzed Hydroamination of Glycals with Dioxazolones**

**General Procedure**: In a glove box, to an oven-dried 10 mL reaction tube which equipped with a magnetic stir bar was added NiBr$_2$·DME (3.1 mg, 0.01 mmol, 5 mol%), L (3.0 mg, 0.01 mmol, 5 mol%), NaI (9.0 mg, 0.06 mmol, 30 mol%) and anhydrous 1,4-dioxane/THF (4:1, 0.6 mL + 0.15 mL). The mixture was stirred
for 10 min, at which time (MeO)₃SiH (102 μL, 0.8 mmol, 4.0 equiv) was added, then glycals (0.2 mmol, 1.0 equiv), 1,4,2-dioxazol-5-ones (0.4 mmol, 2.0 equiv) t-BuOH (57 μL, 0.6 mmol, 3.0 equiv) was added in sequence. The reaction tube was then sealed with a plastic cap, removed from the glove box and stirred at 20 °C for 24 hours maintaining 770 rpm. Afterwards, the resulting mixture was quenched with water (10 mL) and further diluted with ethyl acetate (10 mL). Then the mixture was extracted with ethyl acetate (3x10 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The crude material was separated on a silica gel column affording the desired product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxx.

Acknowledgement

This work was supported by the National Natural Science Foundation of China (22122107).

References


Manuscript received: XXXX, 2023 Manuscript revised: XXXX, 2023 Manuscript accepted: XXXX, 2023 Accepted manuscript online: XXXX, 2023 Version of record online: XXXX, 2023

The Authors

**Left to Right:** Zhenpeng Shen, Guoyin Yin, Yangyang Li

**Left to Right:** Zhenpeng Shen, Guoyin Yin, Yangyang Li

Entry for the Table of Contents
Στερεοσελεκτική Σύνθεση ως 2-Δεοξψ-α-Ν-Γλύκοσιδες φροντισμός Γλύκαλς ω με 1,4,2-Διοξαζολ-5-ονες