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Phenanthroline-Assisted Stereoselective Synthesis of 2-Deoxy Glycosides

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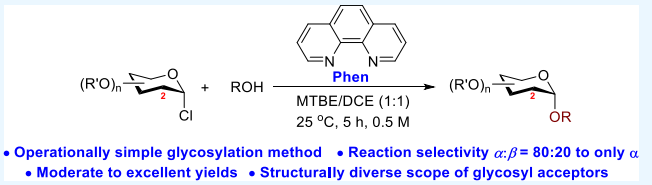
ABSTRACT: The significance of 2-deoxy glycosides in biologically active compounds is well-established, as they frequently play a pivotal role in modulating the efficacy of therapeutic agents. The 2-deoxy sugar embodies a distinctive class of carbohydrates characterized by marked differences in stability, reactivity, and selectivity compared to their counterparts bearing C2-oxygen or other heteroatoms. As a result, the stereoselective synthesis of this carbohydrate class is complicated by its sensitivity to acidic conditions and propensity for hydrolysis and elimination reactions. Furthermore, the lack of C2-oxygen functionality presents an additional challenge in controlling stereoselectivity. In this study, we report the application of commercially available phenanthroline as an effective additive in the stereoselective glycosylation of aliphatic alcohols and phenolic nucleophiles with 2-deoxy glycosyl chlorides, facilitating efficient access to a variety of α-2-deoxy glycosides in high yields with synthetically useful stereoselectivity. Kinetic analyses suggest that phenanthroline plays a crucial role in modulating the selectivity of the reaction.



INTRODUCTION

2-Deoxy sugars, which lack oxygen functionality at the C2 position, constitute a significant class of carbohydrates. Specifically, 2-deoxy and/or 2,6-dideoxy sugars are commonly present in bioactive natural compounds and clinical agents, such as antibiotics, antiparasitics, and anticancer agents.[1] In nature, the structural diversity of 2-deoxy carbohydrates plays a pivotal role in eliciting essential biological activities.[2] Modifying the sugar composition of these 2-deoxy sugars can significantly impact their biological activity.[3] Despite significant progress in innovative glycosylation methodologies, the stereoselective synthesis of 2-deoxy oligosaccharides remains challenging.[4] Several key factors complicate the stereoselective synthesis of 2-deoxy glycosides, including their high reactivity, sensitivity to acidic conditions, and propensity for hydrolysis and elimination reactions. Furthermore, the lack of functional groups at the C2 position presents an additional challenge in controlling stereoselectivity during synthesis.[5] The influence of glycosyl acceptor nucleophilicity on the stereoselectivity of glycosylation reactions involving 2-deoxy thioglycosides and alcohol nucleophiles has been investigated. Notably, glycosyl acceptors characterized by reduced nucleophilicity enhanced the stereoselectivity. This observation illustrates the role that the electronic characteristics of glycosyl acceptors play in modulating glycosylation reaction outcomes.[6]

Methodologies for synthesizing α-2-deoxy-*O*-glycosides involve C2-position defunctionalization to produce the 2-deoxy derivatives through dehalogenation,[7] deamination,[8] and desulfurization processes (Scheme 1a).[9] Although this indirect approach yields a high degree of stereoselectivity, the requirement to modify the functional group at the C-2 position in preparation for subsequent defunctionalization introduces complexity into the synthetic process. Recent advancements in the stereoselective synthesis of α-2-deoxy oligosaccharides have utilized various novel strategies, including the utilization of glycals[10] and readily accessible 2-deoxy glycosyl donors[5,10k,o,s,11] facilitated by metal catalysis, chiral organocatalysts, and the incorporation of remote directing groups (Scheme 1b). Notably, the Galan group has successfully harnessed cyclic silyl-protecting groups to modulate selectivity.[10l] Bennet reported a dehydrative glycosylation method to synthesize 2-deoxy-*O*-glycosides with high α-selectivity (Scheme 1c).[12] The Herzon group reported the nucleophilic attack of glycosyl organolithium, generated in situ, to attain the stereoselective synthesis of 2-deoxy glycosides.[13] In 2023, the Niu group employed palladium catalysts to enhance the activation of leaving groups, thereby achieving a stereospecific synthesis of 2-deoxy-*O*-glycosides through S_N2-like mechanisms (Scheme 1d).[14] Recently, the Jacobsen group reported the use of macrocyclic thiourea catalysts to mediate the β-selective formation of 2-deoxy-*O*-glycosides.[15]

There remains strong interest in developing stereoselective glycosylation methods for 2-deoxy sugars under mild, opera-

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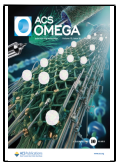
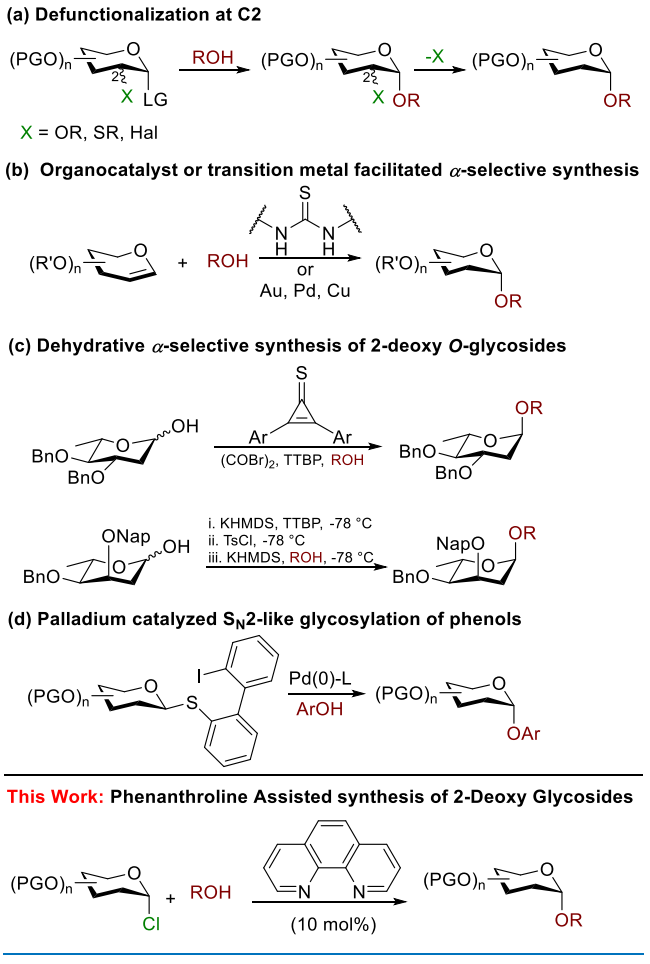


Scheme 1. Strategies for Stereoselective Preparation of α-2-Deoxy-*O*-glycosides



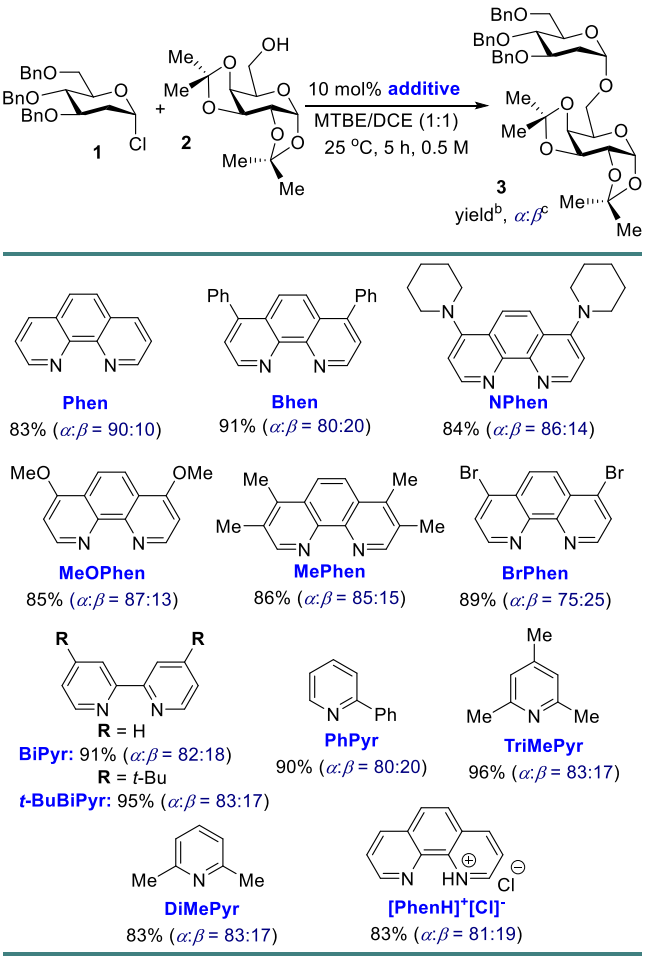
tionally simple conditions that exhibit high efficiency and broad functional group tolerance. Glycosyl halides are widely used as electrophilic donors in glycosylation reactions[16] and hold the potential for the stereoselective synthesis of 2-deoxy-*O*-glycosides. Our group has previously demonstrated that readily available phenanthrolines can function as organocatalysts to stereoselectively synthesize 1,2-*cis* glycosides from pyranosyl and furanosyl bromides.[17] Building on these earlier successes, we hypothesized that phenanthroline could effectively displace the halide leaving group from α-2-deoxy glycosyl chlorides to form the β-phenanthrolinium intermediate, followed by nucleophilic attack to yield the desired α-2-deoxy glycosides. The extension of this strategy to 2-deoxy sugars remains unknown. The 2-deoxy sugar represents a distinct class of carbohydrates that differs significantly from other sugars in terms of reactivity and selectivity. Consequently, our previous phenanthroline protocol for other sugar classes[18] may not produce the same results with the 2-deoxy sugars.

In this study, we present the application of phenanthroline as an additive in the stereoselective synthesis of α-2-deoxy glycosides from various 2-deoxy glycosyl chlorides, which are prepared in situ from their corresponding glycals, along with a variety of alcohols and phenols (Scheme 1). The chloride leaving group was used as a substitution for the previously employed bromide leaving group. This choice is based on the observation that 2-deoxy sugars exhibited markedly lower stability compared to sugars that contain C2-oxygen or other heteroatoms.

RESULTS AND DISCUSSION

We initiated our investigation by selecting 2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride **1** and 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2** as the model coupling partners (Table 1). Given the high reactivity and inherent instability of 2-deoxy glycosyl halides, we generated glycosyl chlorides in situ by reacting the corresponding glycals with HCl, which were used immediately in the glycosylation reaction (see the Supporting Information for their synthesis). The glycosylation reaction involving **1** and **2** was initially conducted utilizing 10 mol % 1,10-phenanthroline (Phen) in a 1:1 solvent mixture of MTBE and DCE. Encouragingly, the initial reaction successfully yielded the desired 2-deoxy disaccharide **3** in 83% yield with α/β = 90:10, favoring the α-isomer. Subsequently, we investigated the impact of phenanthroline derivatives on the reaction's selectivity. We assessed the influence of substituents on the phenanthroline

Table 1. Evaluation of Phenanthroline Additives on the Outcome of the Glycosylation Reaction[a]



[a]All reactions were conducted with donor **1** (0.2 mmol), primary alcohol acceptor **2** (0.10 mmol), and 10 mol % additives with respect to **1** in MTBE/DCE (1:1) at 25 °C at 0.5 M concentration. [b]Isolated yield. [c]Selectivity (α/β) of disaccharide product **3** was determined using ^{1}H NMR.

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scaffold by screening several electron-donating and electron-withdrawing derivatives (Table 1), including BPhen, NPhen, MeOPhen, MePhen, and BrPhen. Unfortunately, no significant increase in α-selectivity was observed in the reaction. Further exploration focused on the necessity of the fused ring system inherent to the catalyst for promoting α-selectivity. This hypothesis was substantiated by substituting 1,10-phenanthroline (Phen) with bipyridine-based cores (BiPyr and *t*-BuBiPyr), an alteration that resulted in diminishing α-selectivity.

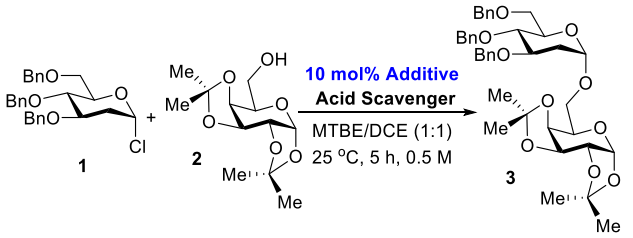
These findings suggest that the rigid fused ring structure of 1,10-phenanthroline is pivotal to achieving optimal selectivity. Additionally, the assessment of pyridine-based additives (Table 1), including 2,4,6-trimethylpyridine (TriMePyr), 2,6-lutidine (DiMePyr), and 2-phenylpyridine (PhPyr), further highlighted the critical role of the two nitrogen atoms present in the 1,10-phenanthroline structure in influencing the selectivity toward the formation of 2-deoxy-*O*-product **3**. Considering that the reaction was conducted in the absence of a stoichiometric acid scavenger, we also sought to elucidate the impact of the singly protonated phenanthrolinium species ($[PhenH]^+[Cl]^-$) that arises during the coupling reaction. The introduction of the phenanthroline salt ($[PhenH]^+[Cl]^-$) resulted in a decrease in the α-selectivity (α/β = 81:19). Finally, we investigated the effects of variations in the loading of the Phen additive, reaction concentration, and solvent choice on the α-selectivity outcomes. Our findings indicate these modifications did not significantly impact α-selectivity (see Tables S1, S2, and S3). Ultimately, 10 mol % of Phen additive in MTBE/DCE (1:1) at 0.5 M concentration at 25 °C was selected as a standard reaction condition. Next, we turned our attention to determining the role of the phenanthroline additive in the glycosylation reaction (Table 2). In the control experiment conducted without the inclusion of the 1,10-phenanthroline additive, the synthesis of disaccharide **3** was achieved with a comparable yield; however, the resulting selectivity was significantly lower (α/β = 70:30, entry 2). This observation underscores the significance of Phen in enhancing α-selectivity.

The introduction of various acid scavengers, such as isobutyl oxide (IBO), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and 4Å MS, resulted in decreased selectivity. This is demonstrated by the observed ratio (α/β = 82:18 − 85:15, entries 3 and 5−6) in contrast to the experiment conducted without an acid scavenger (α/β = 90:10, entry 1). Interestingly, substituting the Phen additive with a stoichiometric amount of isobutyl oxide (IBO) (Table 2, entry 4) produced **3** with selectivity comparable to that observed in the experiment with the Phen additive (Table 2, entry 3). These experiments highlight the critical role of unbound HCl released from glycosyl chloride **1** during its reaction with nucleophile **2** in the presence of a Phen additive and that the introduction of a stoichiometric amount of acid scavengers decreases the effectiveness of the Phen additive as a stereochemistry modulator. Using ($[PhenH]^+[Cl]^-$) yielded product **3** (Table 1) with a yield comparable to that obtained under standard conditions. However, it was observed that the stereoselectivity associated with this approach was somewhat diminished compared to the condition in entry 1 in Table 2. Collectively, these experimental results underscore the importance of 1,10-phenanthroline, along with the presence of unbound HCl, in enhancing the α-selectivity.

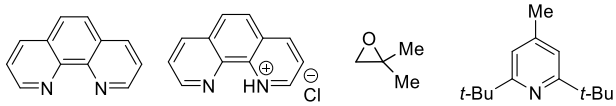
The Lemieux study on halide ion-catalyzed-coupling reactions[18] was applied to evaluate the impact of stoichiometric quaternary ammonium salt on stereoselectivity (Table 2, entries 7 and 8). When the stoichiometric amount of TBAB replaced the Phen additive (entry 7), the yield remained similar, but the selectivity improved (α/β = 86:14), as compared to the control (α/β = 70:30, entry 2). Although this selectivity was slightly lower than observed under Phen-mediated conditions (entry 1), using both Phen and TBAB (entry 8) also yielded **3** with the same selectivity (α/β = 87:13) but still lower than under Phen conditions.

The presence of TBAB enhances the stereoselectivity of the reaction (Table 2, entries 7 and 8). This improvement is likely attributed to the formation of more reactive β-glycosyl bromide species, which upon nucleophilic attack by **2** yield α-glycoside **3** (entry 7, Table 2). When both additives (TBAB and Phen) are included in the reaction (entry 8), TBAB influences stereoselectivity due to its higher concentration. Furthermore, investigations into the role of external HCl demonstrated the significance of unbound HCl released during the reaction, contributing to the observed increase in α-selectivity (Table S4). Additionally, kinetic studies of the reaction between **1** and **2** were conducted in the presence and absence of Phen, with the concentration of product **3** measured at 15 min intervals over 1.5 h (Scheme 2). No notable difference in the rate of product formation was observed, suggesting that Phen does not act as a catalyst but functions as an additive that modulates the selectivity of the

Table 2. Effect of Acid Scavengers and Various Additives



Entry	Additive	Acid Scavenger	Yield (%)[b]	$\alpha:\beta$ ratio[c]
1	**Phen**	None	83	90:10
2	None	None	80	70:30
3	**Phen**	**IBO (2 equiv)**	65	82:18
4	None	**IBO (2 equiv)**	72	80:20
5	**Phen**	**DTBMP (2 equiv)**	74	82:18
6	**Phen**	**4Å MS**	87	85:15
7	Bu_4NBr (2 equiv)	None	76	86:14
8	**Phen** + Bu_4NBr (2 equiv)	None	85	87:13



Phen **[PhenH]⁺[Cl]⁻** **IBO** **DTBMP**

[a]All reactions were conducted with donor 1 (0.2 mmol), primary alcohol acceptor **2** (0.10 mmol), and 10 mol % additives with respect to glycosyl donor **1** in MTBE/DCE (1:1) at 0.5 M concentration at 25 °C. [b]Isolated yield. [c]Stereoselectivity (α/β) was determined by ^{1}H NMR.

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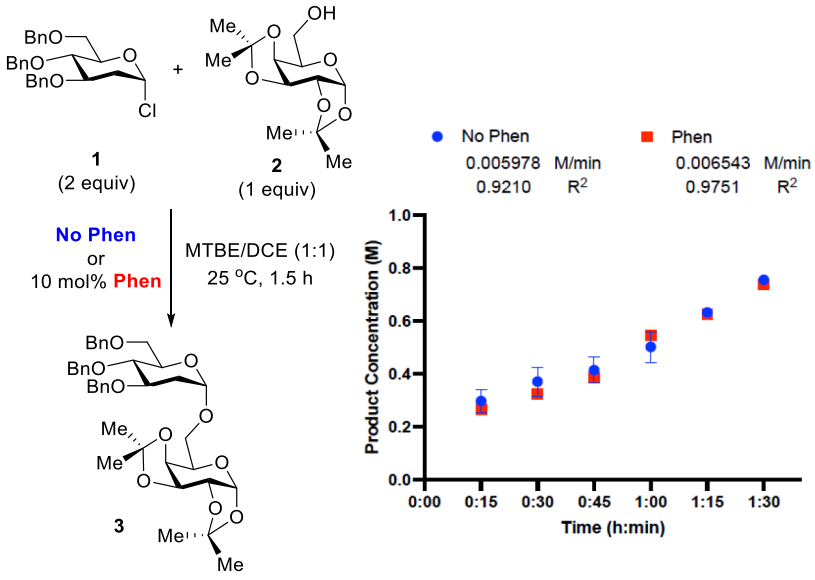
Scheme 2. Kinetic Studies of the Glycosylation Reaction in the Presence and Absence of Phen Additive



reaction (see the Supporting Information for the proposed mechanism).

Next, we evaluated the scope of the common 2-deoxy sugars found in natural products. This evaluation encompassed the incorporation of diverse protecting groups and explored the reactivity of these 2-deoxy motifs with both primary and secondary hydroxyl acceptors (Table 3). Starting with the scope of glycosyl chloride donors (Table 3A and Figure S1), 2-deoxy disaccharides **3**−**7** were obtained in 68−92% yield with α/β ratio varying from 81:19 to the α configuration only, as observed specifically in the case of 2-deoxy galactosyl chloride (product **4**). Considering the recent findings reported by the Galan group, which highlighted an improved α-selectivity utilizing 2-deoxy glycals incorporated with 3,4-fused cyclic protecting groups,[10l] we investigated the scope of glycosyl chlorides bearing 3,4-*O*-disiloxane protecting groups (Table 3A). This strategic modification yielded the corresponding 2-deoxy disaccharides **8**−**11** with significantly higher α-selectivity (α/β = 92:8 − only α) as compared to their benzyl-protected disaccharides **3** and **5**−**7** (α/β = 81:19 − 93:7). These results are consistent with previous findings[10l] that underscores the effectiveness of 3,4-*O*-disiloxane protecting groups in enhancing the α-selectivity of the 2-deoxy glycosylation reactions. Next, we shifted our focus to the nucleophilic acceptor scope (Table 3B and Figure S2). A range of primary and secondary hydroxyl groups proved to be effective coupling partners, producing disaccharides **12**−**19** in 52−91% yields with a high degree of α-selectivity (α/β = 88:12—only α). Biologically relevant noncarbohydrate alcohols, such as serine and menthol, also demonstrated as competent nucleophiles, resulting in 2-deoxy glycosides **20**−**24** in 77−90% yields and with α/β ratio ranging from 89:11 to only α. Additionally, hindered glycosyl acceptors, such as cholestanol and oleanolic acid methyl ester, produced 2-deoxy glycosides **25** and **26** in 71% and 78% yield, respectively, as a single isomer. Moreover, the observed pattern regarding the influence of cyclic protecting groups on the glycosyl chloride donors was consistent across the 2-deoxy D-glucosyl substrates (**14** versus **15** and **20** versus **22**), the 2-deoxy-L-arabinosyl substrate (**16**), and the 2-deoxy-L-rhamnosyl substrates (**17** and **23**), regardless of whether primary or secondary hydroxyl groups were employed in these glycosylation reactions. In these instances, the utilization of 3,4-*O*-disiloxane protecting groups resulted in a high degree of α-selectivity of the glycosylation products. In addition to the tribenzyl and disiloxane substrates, we explored glycosylation using triacetyl 2-deoxy glycosyl chloride. However, this substrate exhibited significantly lower reactivity than its tribenzyl and disiloxane counterparts. As a result, only a minimal amount of the desired product was observed, along with a notable formation of the byproduct 2-deoxy hemiacetal, which arises from the hydrolysis of the starting material, 2-deoxy glycosyl chloride.

Aryl *O*-glycosides are an abundant motif found in natural products and pharmaceuticals.[19] Achieving stereoselective synthesis of such compounds via direct coupling of the glycosyl electrophile and phenol acceptor remains challenging.[20] Therefore, there is a continued interest in the development of synthetic methodologies to access *O*-aryl glycosides stereoselectively.[21] Accordingly, we applied our developed protocol to the stereoselective glycosylations of phenols with 2-deoxy glycosyl halides (Table 4). As expected, 2-deoxy D-galactosyl chloride exclusively provided coupling products **29** and **30** as the α-isomers. In the case of 2-deoxy glucose substrate, the incorporation of the fused cyclic 3,4-*O*-disiloxane protecting group into 2-deoxy glycosyl chloride donors resulted in the formation of the corresponding aryl *O*-glycosides **31** and **32**, which exhibited significantly higher α-selectivity, as compared to the benzyl-protected compounds **27** and **28**, respectively. This result is in agreement with the findings of the Galan group.[10l] However, for the 2-deoxy L-rhamnose substrate that features the 3,4 *O*-disiloxane protecting groups, phenolic acceptors (**34** and **35**, Table 4) demonstrated lower α-selectivity than aliphatic hydroxyl acceptors (**11** and **17**, Table 3). The formation of aryl *O*-glycoside products exhibited relatively modest yields, which can be attributed to the low reactivity of phenol nucleophiles compared with their aliphatic hydroxyl counterparts. Notably, unreacted glycosyl chloride starting materials persisted in the reactions with phenols even after 24 h, indicating incomplete conversion. The increment in the equivalents of phenol acceptors and the extension of the reaction time exhibited

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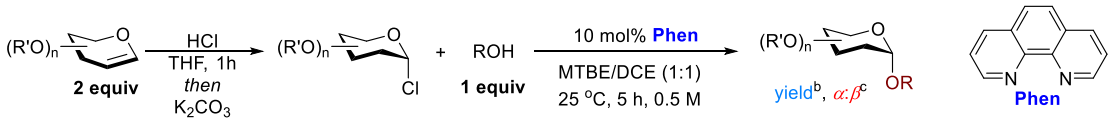
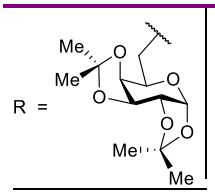
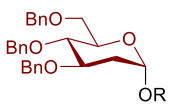
Table 3. Scope of Donors and Acceptors Under Phenanthroline-Assisted 2-Deoxy Glycosylations[a]

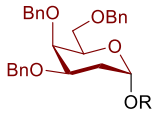


A. Glycosyl Donor Scope

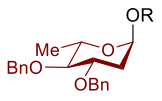




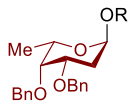
3: 83% ($\alpha:\beta$ = 90:10)



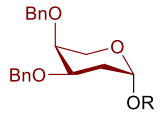
4: 92% (α only)



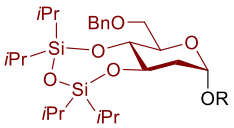
5: 72% ($\alpha:\beta$ = 81:19)



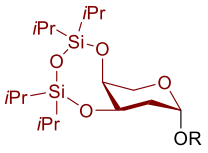
6: 68% ($\alpha:\beta$ = 82:18)



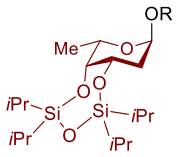
7: 72% ($\alpha:\beta$ = 93:7)



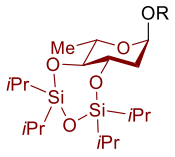
8: 87% ($\alpha:\beta$ = 92:8)



9: 69% (α only)

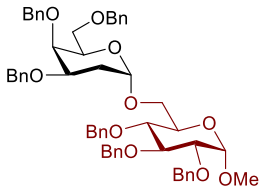


10: 84% (α only)

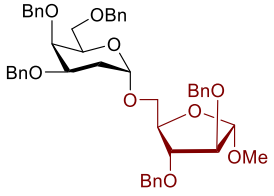


11: 79% ($\alpha:\beta$ = 93:7)

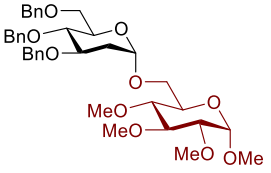
B. Glycosyl Acceptor Scope



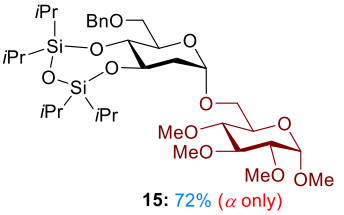
12: 75% (α only)



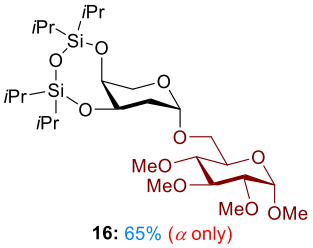
13: 85% (α only)



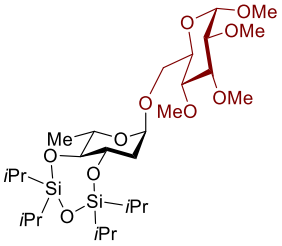
14: 91% ($\alpha:\beta$ = 91:9)



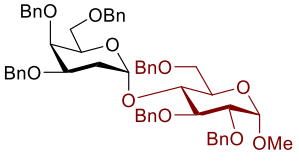
15: 72% (α only)



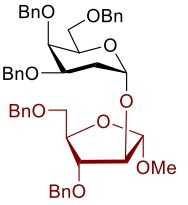
16: 65% (α only)



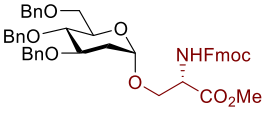
17: 77% ($\alpha:\beta$ = 88:12)



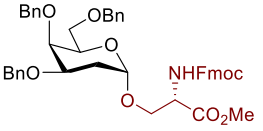
18: 52% (α only)



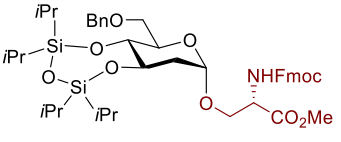
19: 63% (α only)



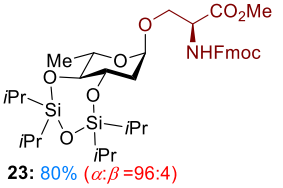
20: 88% ($\alpha:\beta$ = 89:11)



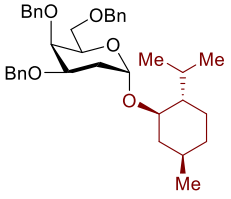
21: 90% (α only)



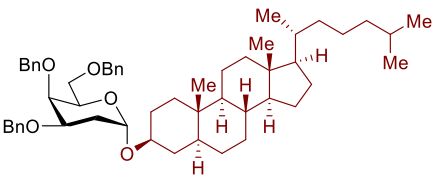
22: 77% (α only)



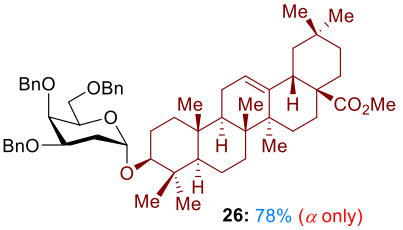
23: 80% ($\alpha:\beta$ =96:4)



24: 86% (α only)



25: 71% (α only)



26: 78% (α only)

[a]All reactions were conducted with glycosyl chloride donor generated in situ from the corresponding glycal (0.2 mmol, 2.0 equiv), alcohol acceptor (0.1 mmol, 1.0 equiv), and Phen (0.02 mmol, 0.1 equiv with respect to glycal) in DCE/MTBE (1:1) at 0.5 M concentration at 25 °C for 5 h. [b]Yields were determined based on isolated products. [c]The (α/β) ratios were determined by ^{1}H NMR analysis for inseparable mixtures of isomers and based on a ratio of isolated isomers in cases wherein separation was successful.

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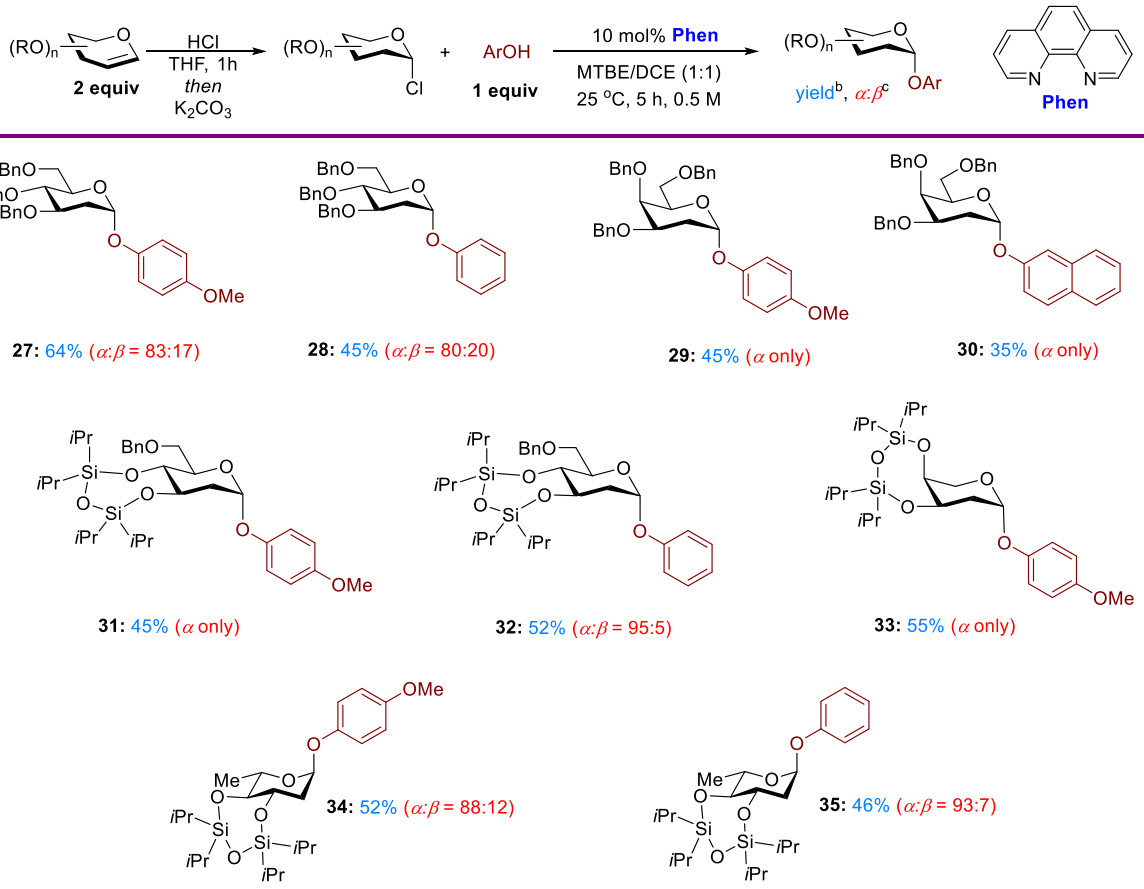
Table 4. Scope of Phenol Glycosyl Acceptors Under Phenanthroline-Assisted 2-Deoxy Glycosylations[a]



[a]All reactions were conducted with glycosyl chloride donor generated in situ from the corresponding glycal (0.2 mmol, 2.0 equiv), alcohol acceptor (0.1 mmol, 1.0 equiv), and Phen (0.02 mmol, 0.1 equiv with respect to glycal) in DCE/MTBE (1:1) at 0.5 M concentration at 25 °C for 5 h. [b]Yields were determined based on isolated products. [c]The (α/β) ratios were determined by ^{1}H NMR analysis for inseparable mixtures of isomers and based on a ratio of isolated isomers in cases wherein separation was successful.

negligible effects on the conversion rates or selectivity of the reactions.

CONCLUSIONS

In summary, we have developed a mild, operationally simple method for the synthesis of 2-deoxy α-glycosides using in situ generated 2-deoxy glycosyl chloride donors from glycals in combination with a substoichiometric amount of 1,10-phenanthroline (Phen) as an additive. This protocol capitalizes on the unique synergistic effect of phenanthroline with the HCl released during the reaction, enabling the efficient production of synthetically useful α-selective products with yields ranging from good to excellent. Our kinetic studies reinforce the significant role of phenanthroline, revealing that while it does not function as a catalyst, it is crucial for attaining selectivity, particularly when working with unbiased 2-deoxy glycosyl chloride donors. This finding highlights the additive's importance in refining glycosylation methodologies and overcoming challenges faced in the stereoselective synthesis of 2-deoxy glycosides. Overall, by integrating an easily accessible additive like phenanthroline, we provide a cost-effective strategy for the synthesis of 2-deoxy glycosides.

MATERIALS AND METHODS

General Experimental Details. All reactions were performed in oven-dried flasks fitted with septa under a nitrogen or argon atmosphere unless otherwise stated. Commercially available starting materials and reagents were used without purification unless otherwise stated. Organic solutions were concentrated by using a Buchi rotary evaporator and a water bath. Thin-layer chromatography (TLC) was carried out with 250 μm glass-backed silica gel plates with a fluorescent indicator (254 nm). TLC plates were visualized with UV light or by submersion in iodine, ceric ammonium molybdate, or 10% sulfuric acid in ethanol, followed by heating on the hot plate. Flash column chromatography was performed using 40−63 silica gel (SiliaFlash F60 from Silicycle). Nuclear Magnetic Resonance (NMR) spectra of all compounds were obtained in $CDCl_3$ (δ 7.26 and 77.00 ppm, respectively) or CD_2Cl_2 (δ 5.32 and 53.84 ppm, respectively) using Bruker 500 MHz or Varian 600 MHz or DRX-400 400 MHz instruments. The chemical shifts (δ) are calculated with respect to the residual solvent peak and are given in ppm. Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). High-resolution mass spectra (HRMS) were obtained on a Micromass LCT Premier XE instrument using electrospray ionization (ESI).

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The following abbreviations are used in experimental glycosylation protocols and optimization procedures: Phen (1,10-phenanthroline), MTBE (methyl *tert*-butyl ether), and DCE (1,2-dichloroethane). Glycal precursors: 3,4,6-tri-*O*-benzyl-D-glucal,[10l] 3,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6-*O*-benzyl-D-glucal,[10l] 3,4-di-*O*-benzyl-L-rhamnal,[22] 3,4-*O*-(1,1,3,3-tetraisopropyldisiloxane-L-rhamnal),[10l] 3,4-di-*O*-benzyl-L-fucal,[23] 3,4.6-tri-*O*-benzyl-D-galactal,[10c] and 3,4-di-*O*-benzyl-L-arabinal[24] were prepared following the literature-reported protocols.

General Procedure for the Phenanthroline-Assisted Glycosylation Reaction. To a solution of glycal (0.2 mmol, 2 equiv) in anhydrous THF (0.5 M) was added HCl (4 M solution in dioxane, 0.1 mL, 0.4 mmol, and 4 equiv), and the reaction mixture was allowed to stir for 1 h. After such time, K_2CO_3 (13.8 mg, 1 mmol, 10 equiv) was added to the reaction mixture, and the resulting suspension was stirred for 1 h, followed by filtration through a pad of Celite. Additionally, the filter cake was washed with dichloromethane. The filtrate was collected and concentrated in vacuo to give crude glycosyl chloride, which was used without further purification. An oven-dried 10 mL Schlenk flask was charged with crude 2-deoxy glycosyl chloride (0.2 mmol, 2.0 equiv), acceptor alcohol (0.1 mmol, 1.0 equiv), 1,10-phenanthroline (0.02 mmol, 10 mmol % with respect to glycosyl chloride), and 0.2 mL of a mixture of methyl *tert*-butyl ether and 1,2-dichloroethane (1:1), and the resulting solution was stirred at room temperature for 5 h. After such time, the reaction mixture was concentrated to dryness and purified by column chromatography on silica gel eluting with hexanes/EtOAc (0 → 40% EtOAc) to give the desired product.

*2-Deoxy-3,4,6-tri-O-benzyl-α-D-galactopyranosyl-(1−6)-1,2,3,4-di-O-isopropylidine-α-D-galactopyranoside (**4**).* Prepared according to the general procedure at room temperature for 5 h. The desired product **4** was obtained as a colorless oil (62.3 mg, 92%, α only) with spectral data identical to that reported in the literature.[10b] **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36−7.27 (m, 14H), 7.26−7.22 (m, 1H), 5.52 (d, J = 5.0 Hz, 1H), 5.04 (d, J = 3.5 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 4.65−4.55 (m, 4H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.31 (dd, J = 5.0, 2.4 Hz, 1H), 3.99−3.92 (m, 4H), 3.75 (dd, J = 10.7, 6.8 Hz, 1H), 3.67 (dd, J = 10.7, 6.4 Hz, 1H), 3.63 (dd, J = 9.3, 7.5 Hz, 1H), 3.55 (dd, J = 9.2, 5.6 Hz, 1H), 2.23 (td, J = 12.2, 3.6 Hz, 1H), 2.05−1.98 (m, 1H), 1.52 (s, 3H), 1.43 (s, 3H), 1.33 (s, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 138.9, 138.6, 138.1, 128.4, 128.21, 128.16, 127.8, 127.6, 127.44, 127.43, 127.3, 109.3, 108.5, 97.5, 96.3, 74.7,74.3,73.4, 72.9,71.1, 70.7, 70.6,70.4, 69.8, 69.2, 65.8, 65.5, 31.1, 26.1, 26.0, 24.9, 24.5. **ESI HRMS:** calcd for $C_{39}H_{48}NaO_{10}$ $[M + Na]^+$, 699.7928; found, 699.7925.

*2-Deoxy-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α-L-fucopyranosyl-(1−6)-1,2,3,4-di-O-isopropylidine-α-D-galactopyranoside (**10**).* Prepared according to the general procedure at room temperature for 5 h. The desired product **10** was obtained as a colorless oil (57.8 mg, 84%, α only). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.52 (d, J = 5.0 Hz, 1H), 4.93 (d, J = 3.5 Hz, 1H), 4.59 (dd, J = 7.9, 2.4 Hz, 1H), 4.33−4.28 (m, 2H), 4.24 (dd, J = 7.9, 2.0 Hz, 1H), 3.97−3.90 (m, 3H), 3.78 (dd, J = 10.0, 6.6 Hz, 1H), 3.55 (dd, J = 10.0, 6.6 Hz, 1H), 2.02 (td, J = 12.4, 3.7 Hz, 1H), 1.84 (dd, J = 12.5, 4.6 Hz, 1H), 1.53 (s, 3H), 1.43 (s, 3H), 1.34−1.30 (m, 6H), 1.22 (d, J = 6.4 Hz, 3H), 1.10−0.87 (m, 28H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 109.0, 108.5, 97.8, 96.3, 73.5, 71.1, 70.64, 70.57, 70.5, 66.7, 66.5, 65.0, 32.9, 26.1, 25.9, 24.9, 24.5, 17.64, 17.59, 17.5, 17.41, 17.394, 17.389, 17.3, 17.23, 17.19, 14.2, 14.1, 13.1, 12.5. **ESI HRMS:** calcd for $C_{30}H_{56}NaO_{10}Si_2$ $[M + Na]^+$, 655.3310; found, 655.3315.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.5c00189.

General information, general experimental procedures for phenanthroline-assisted glycosylation, extended reaction optimizations, proposed mechanism, spectroscopic characterization of all synthesized disaccharides, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

†C.-X.L., C.K.E., and D.A.A. contributed equally. H.M.N. conceived and supervised the project, while C.-X.L. developed the phenanthroline-assisted glycosylation protocol and performed substrate scope studies. C.K.E. performed substrate scope studies. D.A.A. performed additional optimization reactions and substrate scope studies. C.-X.L., C.K.E., and D.A.A. wrote the manuscript and incorporated revisions by H.M.N.

Notes

The authors declare no competing financial interest.

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