

Harnessing Photochemically Generated Sulfenylnitrene for Stereocontrolled 1,2-cis Glycosylations

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Abstract

The stereocontrolled construction of 1,2-cis glycosidic linkages remains a persistent challenge, particularly in furanose systems, where planar oxocarbenium ions permit nucleophilic attack from either face. Conventional thioglycosides, although widely used, typically require harsh activation and often yield poor stereoselectivity. Here, we report a metal-free, photosensitizer-free, blue light-mediated strategy using sulfenylnitrenes as metallomimetic nitrene intermediates to activate thioglycoside donors chemoselectively. Sulfenylnitrene, produced by chemoselective photolysis of S–N bond, enables precise oxocarbenium ion formation, resulting in high 1,2-cis selectivity across ribose, xylose, glucose, galactose, mannose, and the challenging α -2-deoxyribosyl linkages. Cis selectivity is governed by C5–O protecting-group sterics and remotely participating group effects in furanoses, and by conformational locking in pyranoses. This approach allows the efficient synthesis of glycosyl esters, glycopeptides, glycosylated bioactive molecules, and rare 1,2-cis ribopentasaccharides. Notably, the donor design is broadly compatible with alternative activation methods, maintaining high selectivity, and provides a general blueprint for stereocontrolled glycosylation.

Keywords

Sulfenylnitrene, Chemoselective Photolysis, Carbohydrate Chemistry, Stereoselective Glycosylation

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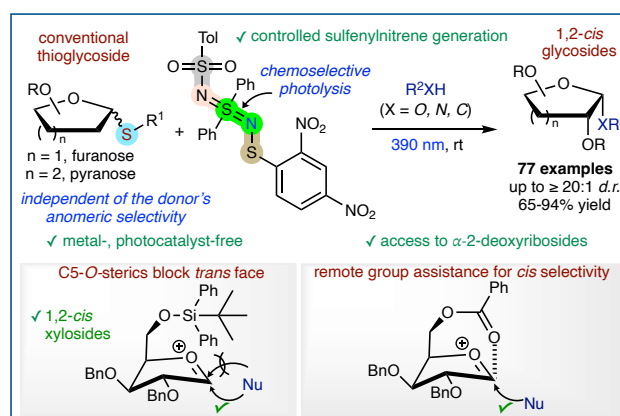
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challenging α-2-deoxyribosyl linkages. *Cis* selectivity is governed by C5–O protecting-group sterics and remotely participating group effects in furanoses, and by conformational locking in pyranoses. This approach allows the efficient synthesis of glycosyl esters, glycopeptides, glycosylated bioactive molecules, and rare 1,2-*cis* ribopentasaccharides. Notably, the donor design is broadly compatible with alternative activation methods, maintaining high selectivity, and provides a general blueprint for stereocontrolled glycosylation.

The controlled generation and use of nitrenes has long fascinated chemists, offering access to highly reactive intermediates capable of enabling diverse bond constructions.¹⁻⁴ Early strategies, including Rh-catalyzed nitrene,^{5,6} Rh, Ir, Co, and Fe-catalyzed acylnitrenes,⁷⁻¹⁰ and silver(I)-catalyzed nitrene transfer,^{11,12} provided versatile platforms for single *N*-atom transfer, C–H amination and aziridination, while iodine (III)-derived iodonitrenes broadened the synthetic scope.^{13,14} Despite these advances, these systems typically rely on precious or redox-active transition metals, whose cost, toxicity, and environmental footprint limit sustainable applications.¹⁵

In this context, sulfur offers a compelling solution. As an earth-abundant element essential to biology, sulfur can function as a metallomimetic centre, capable of accessing diverse oxidation states that mimic metal-like reactivity.¹⁶⁻¹⁸ This tunability enables sulfur to generate three distinct classes of nitrenes, sulfonyl,¹⁹ sulfinyl,²⁰ and sulfenyl,^{17,21,22} each with unique electronic and stereoelectronic properties. While sulfonylnitrenes and sulfinylnitrenes have been explored, the chemistry of sulfenylnitrenes has remained underdeveloped, despite their potential to combine operational simplicity with sustainable reactivity. Importantly, sulfenylnitrenes can be accessed under mild, additive-free conditions, circumventing the dependence on metals or photosensitizers (**Fig. 1a**).¹⁷ Recently, we have utilized sulfenylnitrenes for enabling mild, operationally simple *N*-atom insertion and skeletal editing of *N*-heterocycles with broad functional-group compatibility.¹⁷

Working toward the development of stereoselective glycosylations,²³⁻²⁶ we envisioned that the unique reactivity profile of sulfenylnitrenes (**Fig. 1a**) could be harnessed to activate readily available thioglycoside donors. Thioglycosides are among the most widely employed glycosyl donors,^{24,26} yet their activation typically requires harsh, strong Lewis acidic conditions²⁷ and offers poor stereocontrol. This problem is particularly acute in furanose systems, where rapid epimerization at the anomeric center erodes selectivity²⁸ and continues to frustrate efforts toward a general strategy for *cis* linkages.^{25,29,30} Overcoming this limitation would address one of the longest-standing challenges in carbohydrate chemistry: the stereocontrolled synthesis of 1,2-*cis* glycosidic bonds.³¹ These linkages underpin the structural and functional diversity of natural products, glycoconjugates, and therapeutic agents, yet their reliable construction remains notoriously difficult.³¹⁻³³ The challenge arises from the intrinsic reactivity of oxocarbenium ions: pyranose intermediates are relatively unstable and favor S_N2 pathways,³⁴ whereas the more stable furanose intermediates follow S_N1 pathways, where the planar geometry of the anomeric carbon permits nucleophilic attack from either face (**Fig. 1c**).³⁵⁻³⁷ Consequently, selective access to 1,2-*cis* linkages is particularly problematic in furanose systems. Existing approaches, particularly for pyranoses, such as intramolecular aglycone delivery,³⁸ remote group participation,³⁹ or conformational locking,^{40,41} often rely on elaborate donor designs,^{23,42,43} cryogenic

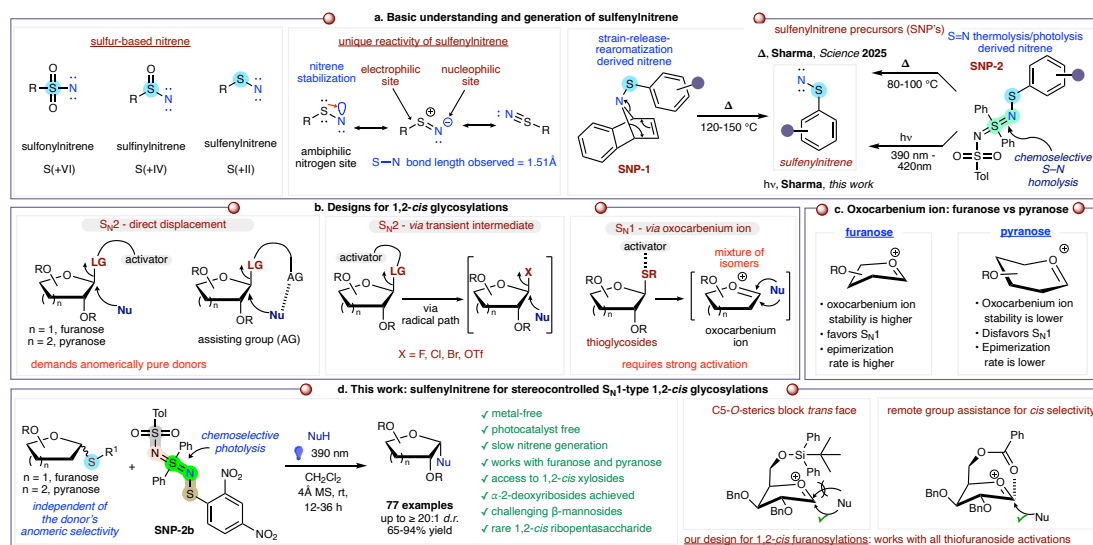


Fig. 1 | Sulfenylnitrenes and their application in 1,2-*cis* glycosylations. (a) sulfur-based nitrenes, the unique reactivity of sulfenylnitrene, and its mode of generation. (b) established 1,2-*cis* glycosylation strategies and their pitfalls. (c). Features of oxocarbenium ion: furanose and pyranose. (d) **This work**: sulfenylnitrene for stereocontrolled S_N1-type 1,2-*cis* glycosylations.

conditions,³¹ and expensive metal catalysts⁴² that compromise generality (**Fig. 1b**).

Here, we present a metal-free, photosensitizer-free strategy in which blue light enables chemoselective photolysis of a one S–N bond in sulfenylnitrene precursor to generate sulfenylnitrenes that enable mild, Lewis acid-free activation of conventional thioglycoside donors (**Fig. 1d**). This approach overcomes longstanding stereochemical barriers, providing efficient access to 1,2-*cis* linkages across both pyranose and furanose series. Mechanistic studies revealed that steric or chelating substituents at C5 act as a general design principle for furanoses, directing *cis* selectivity by blocking the *trans* face. Notably, the donor design remains effective under diverse activation conditions, yet consistently delivers high 1,2-*cis* selectivity. The synthetic potential of this platform is showcased in the glycosylation of bioactive molecules and the streamlined assembly of a 1,2-*cis* ribopentasaccharide. More broadly, this work introduces sulfenylnitrenes as a sustainable class of metallomimetic intermediates, while establishing a unifying donor-design principle for one of carbohydrate chemistry's most persistent challenges. Beyond glycoscience, these findings outline a general blueprint for exploiting sulfur-based nitrenes in selective bond construction.

Results and discussion

Reaction development

We began by examining conditions for sulfenylnitrene generation using thioglycoside donor **1a**. Thermal activation of sulfenylnitrene precursors (SNP-1 and SNP-2) successfully decomposed **1a**, but predominantly through unproductive pathways (**Fig. S4** in SI). This limitation prompted us to explore chemoselective S–N

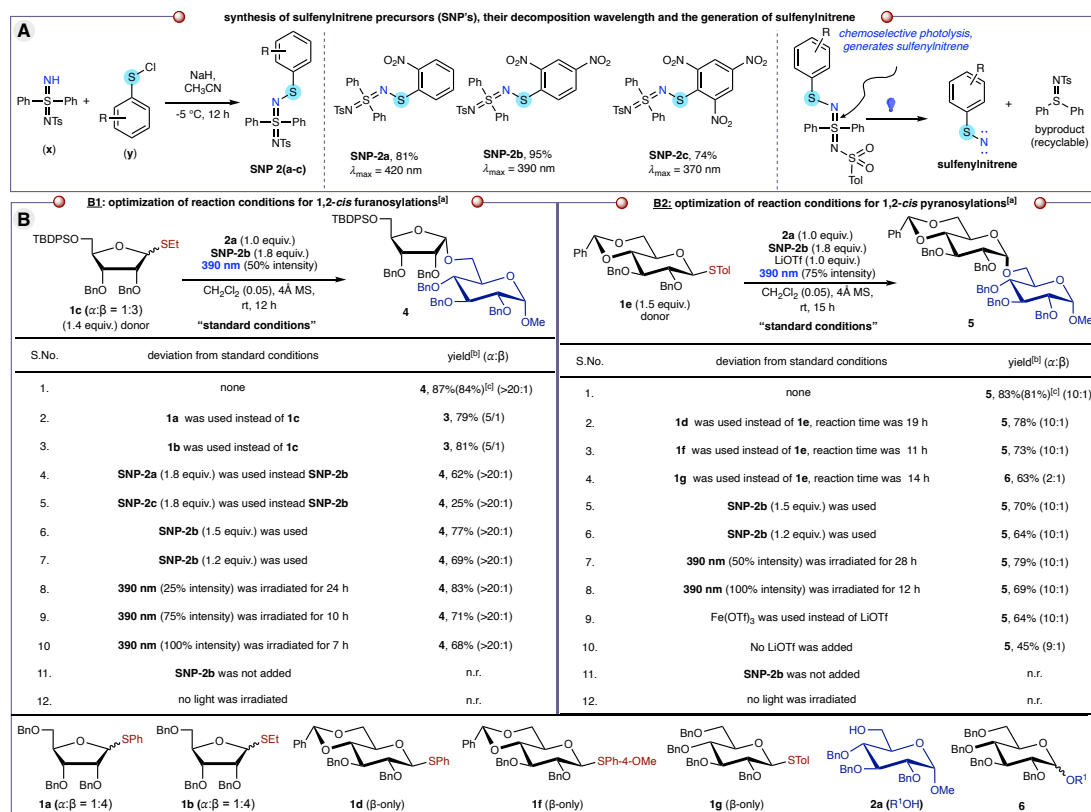


Fig. 2 | Reaction development for sulfenylnitrene-mediated 1,2-*cis* glycosylations. (A) synthesis of sulfenylnitrene precursors [SNP-2(a-c)], their decomposition wavelengths, and a chemoselective S–N photolysis. (B) Optimization of reaction conditions for 1,2-*cis* glycosylations. [a] Reactions were conducted with acceptor **2a** (0.026 mmol), donor **1** (**a-g**) (0.036 mmol), SNP-2 (0.047), blue-light (390–440 nm), and CH₂Cl₂ (0.05 M). [b] Yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yields, **note**: ¹H-NMR of the crude reaction mixture was analyzed to determine the diastereoselectivity. Ph, phenyl; Ts, tosyl; TBDPS, *tert*-butyldiphenylsilyl; Bn, benzyl; Et, ethyl; MS, molecular sieves; SNP, sulfenylnitrene precursor; Tol, tolyl; n.r., no reaction.

bond photolysis in SNP-2, which generates sulfenylnitrenes under mild and neutral conditions. To further tune reactivity and absorption characteristics, we designed a family of precursors, SNP-2(a-c), that undergo clean photolysis across 370–420 nm (Fig. 2A).¹⁷ Consequently, changing from thermal to photochemical conditions was fruitful in providing the desired glycosidic linkages by activating **1a** (Fig. S4 in SI).

Using these, we optimized conditions for 1,2-*cis* furanosylation (Fig. 2B1). The engineered thiofuranoside donor **1c**²⁴ (1.4 equiv.) with acceptor **2a**, SNP-2b, CH₂Cl₂ (0.05 M), and 4 Å MS afforded disaccharide **4** in 84% yield with excellent stereocontrol (α:β = >20:1). The C5 protecting group was decisive: replacing TBDPS with Bn in donors **1a** or **1b** attenuated selectivity, underscoring the steric design of **1c**. SNP variants (SNP-2a, SNP-2c) maintained selectivity but reduced yields, highlighting the balance between precursor photophysics and productive glycosylation. Control experiments confirmed that both light and the SNP activator were indispensable, as reactions in their absence returned only starting material.

In parallel, we optimized 1,2-*cis* pyranosylation (Fig. 2B2). Donor **1e** (1.5 equiv.)

and acceptor **2a** with **SNP-2b** (1.8 equiv.) and LiOTf as oxocarbenium stabilizer furnished disaccharide **5** in 81% yield and excellent stereocontrol ($\alpha:\beta = >10:1$) under 390 nm blue LED irradiation. Alternative thiopyranosides (**1d**, **1f**) gave comparable outcomes, though with slightly varied reaction times, depending on the thioaryl substituent, underscoring the generality of donor design. Protecting-group patterning proved critical: replacing the 4,6-benzylidene with 4,6-di-*O*-Bn sharply diminished both yield and stereocontrol ($\alpha:\beta = 1:1$), consistent with the conformational “locking group” effect.^{40,41} Variation in **SNP-2b** loading identified 1.8 equiv. as optimal, while light-intensity studies consistently showed that too little flux slowed reactions and too much eroded efficiency. Substituting Fe(OTf)₃ for LiOTf preserved stereocontrol but reduced yields, underscoring the unique stabilizing role of lithium and triflate counterions. Collectively, these studies establish that precise control of nitrene flux, donor architecture, protecting-group conformation, and counterion effects provides a unified blueprint for high-fidelity 1,2-*cis* glycosylations across both furanose and pyranose frameworks. With these optimized conditions, we next explored the generality of this sulfenylnitrene platform across a broad range of glycosyl donors and acceptors.

Substrate scope studies

With the viability of sulfenylnitrene activation established, we next explored its generality across furanosyl and pyranosyl donors (**Figs. 3-4**).

Furanosylations. Ribose donor **1c** coupled efficiently with both primary and secondary alcohols, ranging from simple glucose and mannose acceptors to sterically demanding tertiary alcohols and carboxylic acids, all delivering *cis*-selective disaccharides **7-17**. Alkyne- and aryl-acid-containing partners were also tolerated, underscoring the orthogonality of this activation mode. Xylose donor **1h**, which typically suffers from competing oxocarbenium conformations,⁴⁴ furnished *cis* products **18-25** with high fidelity, while arabinose donors (**1j-1k**) showed similarly robust behavior **31-32**.^{37,44} Importantly, the challenging 2-deoxy-ribose **1i** system was addressed through C5-OTBDPS substitution, which enforced α -selectivity across diverse acceptors **26-30**. Even non-oxygen nucleophiles proved competent, as allyltrimethylsilane and sulfonamides yielded C- and N-glycosides with high stereocontrol (**33-34**) (**Fig. 3**).

Pyranosylations. Extension to pyranoses revealed uniformly high reactivity and stereocontrol across glucosyl, galactosyl, and even notoriously difficult β -mannosyl donors (**Fig. 4**). Primary, secondary, and carboxylic acid acceptors all coupled smoothly, providing *cis* products in consistently high yields (**35-52**). Notably, sulfenylnitrene activation enables direct β -mannosylation,⁴¹ complementing specialized existing approaches.

Collectively, these results establish sulfenylnitrene activation as a general and stereocontrolled method for constructing 1,2-*cis* linkages across both furanose and

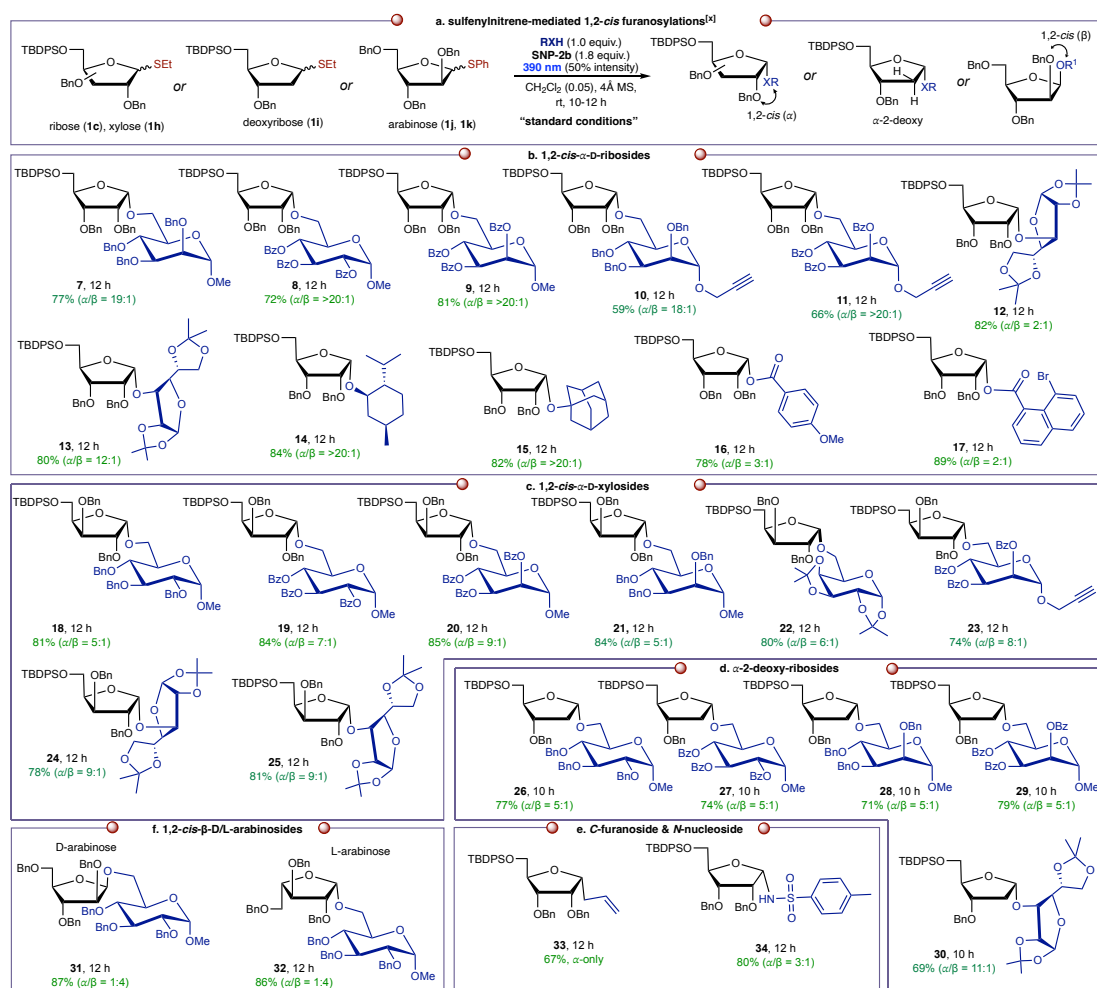


Fig. 3 | Scope of sulfenylnitrene-mediated 1,2-*cis* furanosylations. (a) General scheme for 1,2-*cis* furanosylations. (b) Scope of 1,2-*cis* ribosides. (c) Scope of 1,2-*cis* xylosides. (d) Scope of α-2-deoxy-ribosides. (e) Scope of C-furanoside and N-nucleoside. (c) Scope of 1,2-*cis* xylosides. [x] Reactions were conducted with acceptor (0.026 mmol), donor **1** (**c**, **h-k**) (0.036 mmol), **SNP-2b** (0.047), blue-light (390 nm, 50% intensity), and CH₂Cl₂ (0.05 M). **Note:** ¹H-NMR of the crude reaction mixture was analyzed to determine the diastereoselectivity. Ph, phenyl; Ts, tosyl; TBDPS, *tert*-butyldiphenylsilyl; Bn, benzyl; Et, ethyl; MS, molecular sieves; SNP, sulfenylnitrene precursor; Tol, tolyl.

pyranose series. The breadth of tolerated donors and nucleophiles, including alcohols, acids, and even C- and N-nucleophiles, highlights the robustness of this chemistry, while direct access to β-mannosides and deoxyfuranosides underscores its synthetic distinctiveness.^{40,41}

Applications to complex substrates and oligosaccharide synthesis. Having established the breadth of the scope, we next challenged the sulfenylnitrene activation with complex and bioactive molecules (**Fig. 5a**). Glycopeptide construction is particularly demanding,⁴⁵ yet ribosyl donor **1c** coupled efficiently with serine hydroxyl groups to furnish O-ribosylated derivatives **53-54** (NHBoc and NHCbz protected) and with alanine carboxyl groups to afford C-ribosylated products **55-56**, all in high yields and stereocontrol. Moving beyond amino acids, steroid frameworks proved equally compatible. Ribosyl donor **1c** coupled smoothly with cholesterol and oleanolic acid to

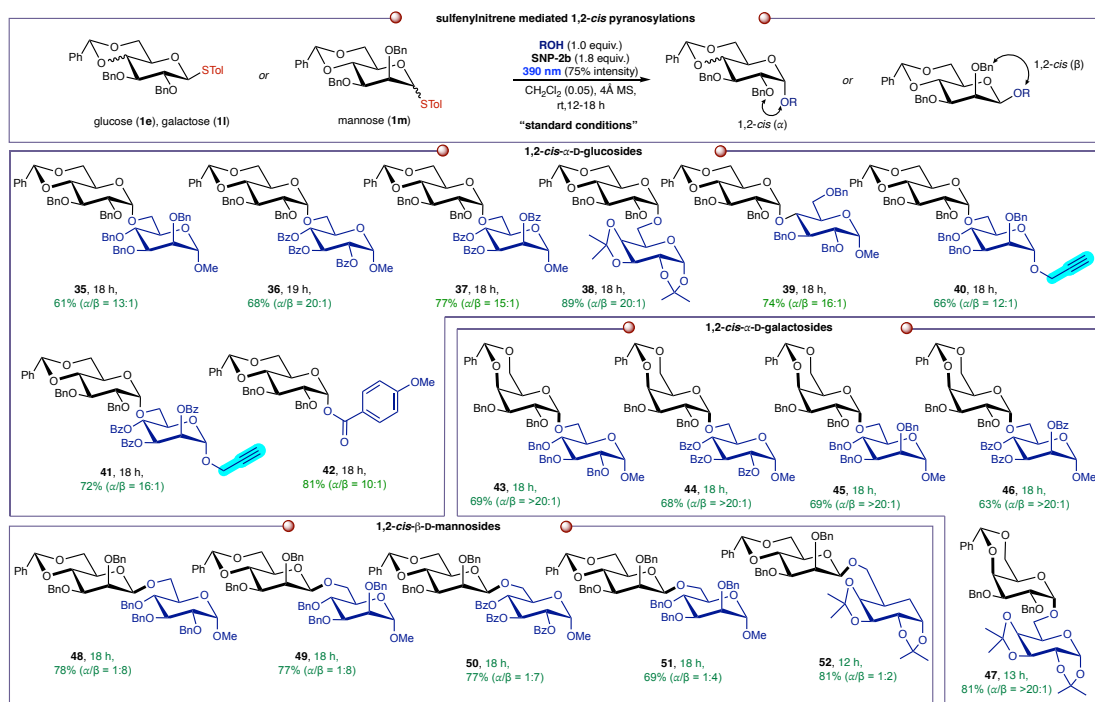


Fig. 4 | Scope of sulfinylnitrene-mediated 1,2-*cis* pyranosylations. (a) General scheme for 1,2-*cis* pyranosylations. (b) Scope of 1,2-*cis*-α-D-glucosides. (c) Scope of 1,2-*cis*-α-D-galactosides. (d) Scope of 1,2-*cis*-β-D-mannosides. [x] Reactions were conducted with acceptor (0.026 mmol), donor **1** (e, l-m) (0.036 mmol), **SNP-2b** (0.047), blue-light (390 nm, 75% intensity), and CH₂Cl₂ (0.05 M). **Note:** ¹H-NMR of the crude reaction mixture was analyzed to determine the diastereoselectivity. Ph, phenyl; Ts, tosyl; Et, ethyl; MS, molecular sieves; SNP, sulfinylnitrene precursor; Tol, tolyl.

provide glycoconjugates **57-58** with excellent *cis* selectivity. Notably, the methodology was directly applied to clinically relevant small molecules. Ribosylated ciprofibrate (**59**), a lipid-lowering drug, was obtained in good yield and selectivity, while dehydrocholic acid, a therapeutic for liver and biliary disorders, furnished the corresponding riboside **60** efficiently. Nucleoside analogues were also accessible: 2-deoxy and 2,3-deoxy-3-azido thymidine derivatives underwent productive coupling to give ribosylated thymidines **61-62**. In addition, the sulfonamide-based drug topiramate was glycosylated cleanly to provide conjugate **63**. Finally, extending the donor series beyond ribose, glucosyl donor **1e** successfully delivered glucosylated oleanolic acid **64** in high yield and selectivity. Together, these examples underscore the capacity of the method to access glycopeptides, glycoconjugates, glyconucleosides, and glycodrugs with operational simplicity and stereochemical precision.

Encouraged by this reactivity, we turned to oligosaccharide synthesis, where 1,2-*cis* motifs remain a longstanding challenge.⁴⁶ Iterative couplings of ribosyl donor **1c** enabled the construction of a ribopentasaccharide **70** with uniformly high 1,2-*cis*-selectivity (**Fig. 5b**). Importantly, the first disaccharide was prepared on a one mmol scale, highlighting the scalability of the transformation. Each successive coupling

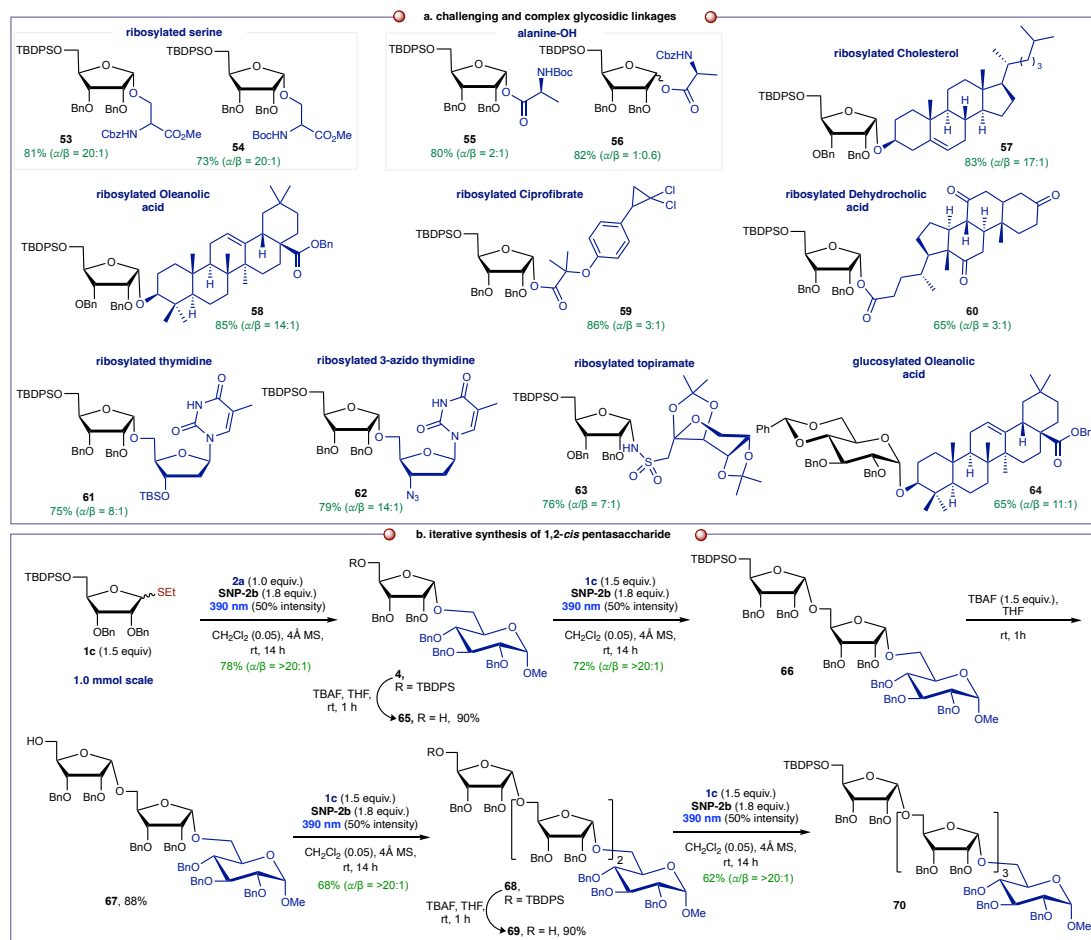


Fig. 5 | Application of sulfenylnitrene-mediated 1,2-*cis* glycosylation strategy (a) Scope of challenging and complex glycosylated linkages. (b) Iterative synthesis of 1,2-*cis* ribopentasaccharide, including 1.0 mmol scale. proceeded in good to excellent yields and stereoselectivity, establishing a streamlined route to a rare *cis*-rich oligosaccharide.

In summary, these applications highlight the power of sulfenylnitrene activation to extend beyond model systems into peptides, steroids, nucleosides, drugs, and higher glycans. This broad functional group tolerance, coupled with the ability to deliver complex 1,2-*cis* architectures at scale, firmly establishes the methodology as a versatile platform for carbohydrate chemistry. Having demonstrated synthetic utility, we next turned to mechanistic investigations to elucidate the origins of selectivity.

Mechanistic investigations

Role of C5 protecting groups: To probe the origins of stereocontrol, we first examined the influence of C5 protecting groups on ribosyl donors (**Fig. 6a**). Donors bearing C5-OMe (**1n**) or C5-OBn (**1a**) underwent sulfenylnitrene activation to afford disaccharides **3** and **71** in high yields with strong *cis*-selectivity. This outcome is consistent with the conformational bias of the transient oxocarbenium ion, which favors *cis*-face attack and furnishes kinetically controlled 1,2-*cis* products.⁴⁴ In contrast, activation of analogous thioglycosides under Lewis acidic conditions produced

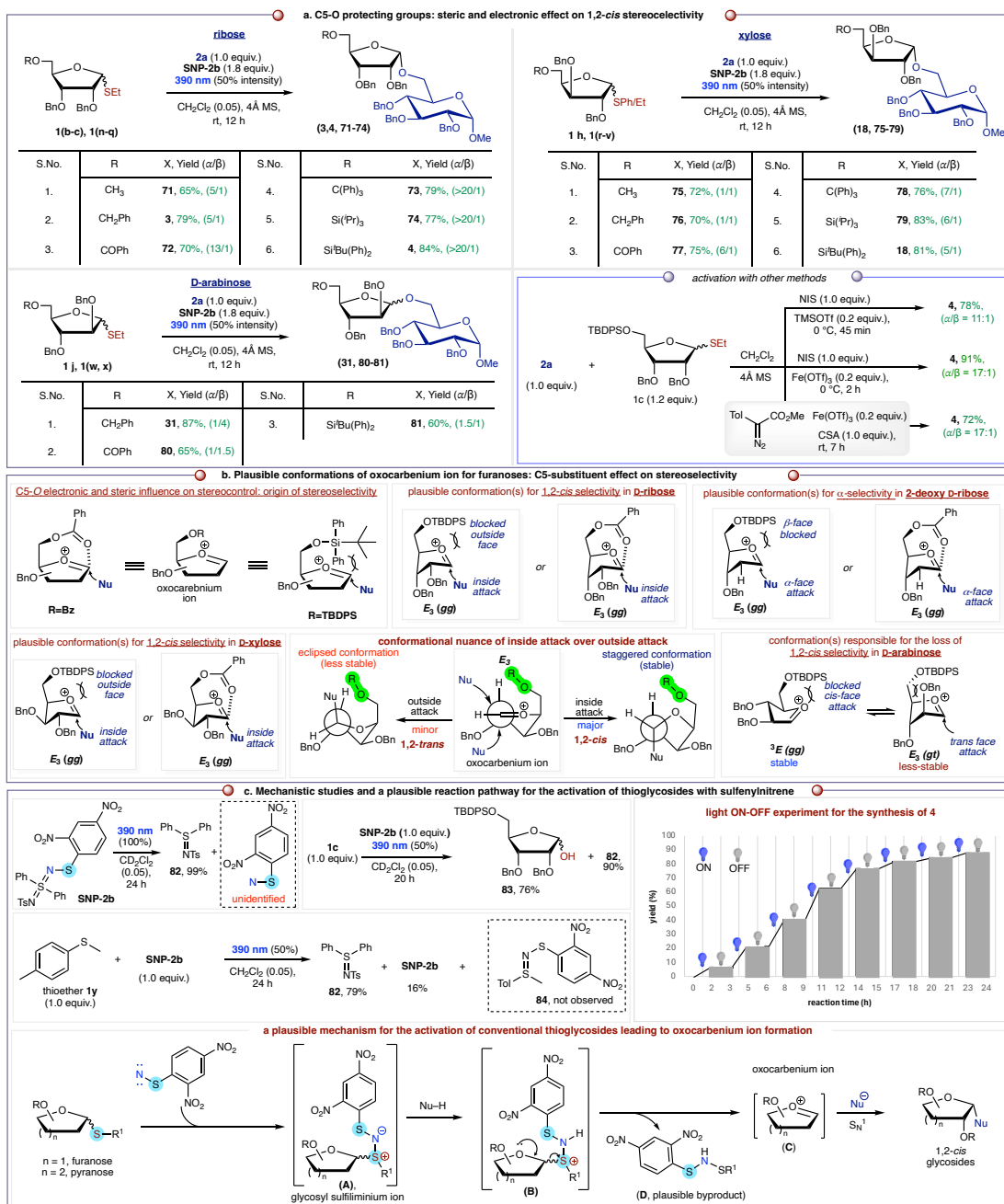


Fig. 6 | Mechanistic studies for the induction of 1,2-*cis* stereoselectivity. (a) The effect of C5-O protecting groups on the induction of *cis* selectivity, and the activation of our designed donor with the established thioglycoside activation method. (b) The conformational explanation for the induction of 1,2-*cis* selectivity, and the importance of inner face attack in Newman projection of a stable conformer of oxocarbenium ion. (c) Mechanistic studies for the activation of conventional thioglycosides using sulfonylnitrenes. gg, gauche-gauche; gt, gauche-trans. extensive epimerization at the anomeric center, highlighting the mildness and stereochemical fidelity of sulfonylnitrene activation.²⁸ Expanding to electronically distinct and sterically demanding groups, the C5-OBz donor (**1o**) gave excellent yields with enhanced *cis*-selectivity **72**. We attribute this to a remote group effect,³⁹ wherein the benzoyl substituent disfavors the *trans*-face approach through an anchimeric-type interaction.³¹ Further increasing steric bulk with C5-OTrt (**1p**), OTIPS (**1q**), and

OTBDPS (**1c**) substituents maintained excellent selectivity, confirming that large groups at C5 reinforce *cis* outcomes in ribose (**4**, **73-74**).

By contrast, xylosyl donors exhibited different behavior. Whereas ribose derivatives inherently favor *cis* products, xylose donors with small substituents, such as C5-OMe (**1r**) or C5-OBn (**1s**), produce nearly equimolar mixtures of anomers **75-76**, reflecting their intrinsic conformational flexibility.³⁷ Introduction of a benzoyl group (**1t**), however, restored high *cis* selectivity **77** through the same remote group effect³⁹ as observed in ribose. Likewise, bulky substituents such as trityl (Trt, **1u**), TIPS (**1v**), and TBDPS (**1h**) yielded high *cis*-selective products **78-79**, **18**, with trityl providing marginally superior control over the silyl groups.

A complementary picture emerged for arabinose donors, where the spatial orientation of the C5 substituent favored the opposite oxocarbenium ion conformation. For instance, the C5-OBn donor (**1j**) furnished high yields of **31** with good *cis* (β) selectivity, whereas C5-OBz (**1w**) slightly diminished this selectivity **80** through electronic effects.³⁹ Strikingly, increasing steric demand with C5-OTBDPS (**1x**) significantly reversed the stereochemical outcome **81**, favouring the *trans*-anomer, underscoring the profound impact of C5 steric effects in arabinose.

Taken together, these studies reveal that stereoselectivity in furanosylation is finely modulated by the steric and electronic properties of the C5 substituent. While ribose, xylose, and 2-deoxy ribose donors are predisposed toward *cis*- or α -selective outcomes under sulfonylnitrene activation, arabinose sugars provide a unique case where steric congestion at C5 can invert the stereochemical course. Importantly, unlike Lewis acid activation, sulfonylnitrene-mediated conditions preserve these inherent preferences without anomeric scrambling, offering a powerful handle for predictable stereocontrol.

Activation of our donor with other activation methods: To benchmark our system, we next examined the activation of model donor **1c** under established conditions. Treatment with NIS/TMSOTf furnished the disaccharide product with high *cis* selectivity; however, careful monitoring and short reaction times were required to suppress the epimerization commonly associated with strong Lewis acid activation.²⁸ Activation with our NIS/Fe(OTf)₃ protocol²⁴ delivered the same high *cis* selectivity, in excellent agreement with the outcome of sulfonylnitrene activation. Finally, application of iron-carbene-mediated activation²⁶ likewise afforded the *cis* product as the major isomer. Collectively, these results demonstrate that the stereochemical influence of the C5 substituent is preserved across diverse activation modes, underscoring its central role in governing selectivity at the anomeric center.

The origin of stereocontrol differs between pyranose and furanose systems. In pyranoses, the mechanistic basis for 1,2-*cis* selectivity with conformationally locked protecting groups has been extensively described by Crich and co-workers.^{40,41} In contrast, the furanose case is less understood.^{25,29,30} Our studies reveal that C5 sterics

and electronics play a decisive role in dictating face selectivity of the oxocarbenium ion (**Fig. 6b**). For ribose, the oxocarbenium ion predominantly adopts the E₃ (*gg*) envelope conformation, favoring inside attack (*cis* product). C5 substituents align towards the electron-deficient C1 center, blocking the trans face and stabilizing the cation. Minor trans products arise from less stable conformations (⁴T₃ (*gg*), ⁴E (*gg*), ³E (*gg*)) as supported by prior work from Woerpel^{35,37,44} and Codée^{37,44} (**Fig. S7** in SI). Similarly, 2-deoxyribose also prefers the E₃ (*gg*) envelope, where steric shielding of the β-face enforces α-selectivity. In xylose, the dominant E₃ (*gg*) and ⁴T₃ (*gg*) conformations rationalize the observed high *cis* selectivity with minor trans formation. In contrast, arabinose predominantly adopts the ³E (*gg*) conformation, which initially promotes *cis* selectivity; however, C5 steric/electronic influences can redirect the system into an E₃ (*gg*) envelope, leading to competing *trans* selectivity. Overall, these combined studies highlight that sulfenylnitrene-mediated activation proceeds through a distinct sulfiliminium-sulfonium-oxocarbenium ion pathway, and that the C5 steric and electronic environment in furanosyl oxocarbenium ions is the dominant factor controlling the remarkable stereoselectivity.

To probe the mode of activation, we first irradiated **SNP-2b**, which predominantly furnished sulfinimine **82**, while the expected nitrene fragment remained elusive. When the ribose donor **1c** was subjected to identical conditions in the absence of nucleophiles, the hydrolyzed donor **83** and sulfinimine **82** were obtained as major products. A thioether model (tolyl methyl sulfide, **1y**) failed to deliver any sulfilimide **84** under identical photoactivation, instead producing only sulfinimine **82**. This finding highlights the unique reactivity of sulfenylnitrene with thioglycosides and indicates that simple thioethers are unreactive. Importantly, light ON-OFF experiments confirmed that continuous irradiation is required, consistent with a photogenerated nitrene as the initiating species.

Together, these observations support the mechanistic proposal shown in **Fig. 6c**. Photoexcited **SNP-2b** generates sulfenylnitrene, which engages thioglycosides to form glycosyl sulfiliminium ion **A**. This intermediate undergoes rearrangement to sulfonium ion **B**, whose fragmentation, assisted by the ring oxygen, delivers the key oxocarbenium ion **C** along with byproduct dithiohydroxylamine **D**. The oxocarbenium ion **C** then undergoes stereocontrolled nucleophilic attack, governed by conformational and protecting-group effects, to furnish highly *cis*-selective glycosides.

Conclusion

In summary, we establish a general strategy for stereocontrolled furanosylation and pyranosylation by harnessing sulfenylnitrene-mediated activation of easily accessible conventional thioglycoside donors. This mild, metal-free approach enables direct access to 1,2-*cis* glycosidic linkages, long recognized as a central challenge in

carbohydrate chemistry, across a broad spectrum of nucleophiles and donor classes with consistently high selectivity. Mechanistic analysis reveals a striking divergence between furanoses and pyranoses. In furanoses, C5 protecting groups emerge as decisive stereocontrolling elements, biasing oxocarbenium conformations and enforcing predictable *cis* or high α -selective outcomes. Pyranoses, by contrast, follow classical stereoelectronic preferences, yet sulfonylnitrene activation preserves their inherent selectivity without the scrambling typically associated with Lewis acid catalysis. This fidelity highlights the unique advantage of sulfonylnitrene activation: it amplifies intrinsic donor features while suppressing competing pathways. Beyond providing a practical route to otherwise elusive glycosidic architectures, these findings introduce a C5-governed paradigm of furanose stereocontrol and a scrambling-free activation principle for pyranoses. Together, they expand the conceptual framework of glycosylation chemistry and open new avenues for donor design and the synthesis of nucleosides, glycoconjugates, and medicinally relevant oligosaccharides.

Online content

Any methods, additional references, research reporting summaries, source data, extended data, supplementary information, acknowledgements, details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org>.

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Methods

General Procedure for the activation of conventional thioglycoside by sulfonylnitrene for stereoselective 1,2-*cis* furanosylations:

To a 4 ml screw-capped vial that contained a magnetic stir bar was sequentially added a conventional thioglycoside **1(a-x)** (40.0 μmol , 1.4-1.5 equiv.), a nucleophile **2** (25.0 μmol , 1.0 equiv.), **SNP-2b** (45.0 μmol , 1.8 equiv.), 4 Å molecular sieves (100 wt%) and CH_2Cl_2 (0.05M) under ambient conditions. The vial was tightly sealed with a Teflon-lined cap and allowed to stir for 10-18 h at room temperature, with irradiation from a 40 W, 390 nm blue LED (50-75% intensity) placed ~6 cm on the right side. Upon complete consumption of nucleophile, the reaction mixture was then quenched by the addition of aq. sat. NaHCO_3 . The organic layer was separated, and the aqueous layer was washed with ethyl acetate (2 times). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a pad of cotton and solvents were removed under reduced pressure. The residue was purified by silica gel chromatography to give the desired product.

Data availability

The authors declare that all data supporting the findings of this study are available in this manuscript and its Supplementary Information files.

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Author contributions

I.S. and S.P.S. conceived the activation method and the C5-effect. S.P.S., P.K., and U.C. synthesized the donors. S.P.S. expanded the scope to both classes of sugars, performed late-stage glycosylations, and assembled the pentasaccharides. S.P.S. and I.S. wrote the manuscript. All authors discussed the results and approved the final version.

Additional information

Supplementary information: The online version contains supplementary material available at <https://doi.org>

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