ChemComm



COMMUNICATION

View Article Online

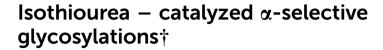


Cite this: Chem. Commun., 2025, **61**, 3856

Received 14th October 2024 Accepted 6th January 2025

DOI: 10.1039/d4cc05456c

rsc.li/chemcomm



Bhaswati Ghosh, ‡ Charles Enlow, ‡ Zhichen Ma, Ashley N. Warden and Abram J. Axelrod (1) *ab

Herein, we present a catalytic strategy to efficiently form both α -1,2-cis and α -1,2-trans glycosyl linkages from either glycosyl bromide or chloride donors using the commercially available HyperBTM isothiourea in both good yields and selectivities.

Exerting stereocontrol in glycosylation is a fundamental goal within carbohydrate synthesis and is highly important for the efficient preparation of single-isoform oligosaccharides, enabling their interrogation in glycobiology and medicine. Considering the numerous variables inherent to glycosidic bond formation, the preparation of complex oligosaccharides remains a challenging endeavor. Accordingly, the development of methodologies that enable high degrees of stereocontrol have been an historical objective overall,² and notably in the context of α -linked glycosides. While the synthesis of α-1,2-trans glycosides is often realized through anchimeric assistance with protecting groups, forming α-1,2-cis glycosides is less predictable due to stereoelectronic factors promoting a fluid S_N1 and S_N2 continuum.³ Historically, α-1,2-cis selectivity has been accomplished through the stoichiometric use of halide-ion, pyridine, amine, and phosphine nucleophiles, often requiring extended reaction times for full conversion. Numerous tactics have subsequently been advanced including the use of auxiliaries, 8 directing groups, 9 and exogenous modulators.¹⁰ Recently, α-1,2-cis glycosides have been prepared utilizing transition-metal catalysis 11,12 or with maingroup reagents. 13,14 However, despite these advances, drawbacks exist regarding catalyst loadings, and specialized glycosyl donors. Additionally, requirements for high-dilution conditions and/or cryogenic temperatures are needed to ensure selectivity, and in the context of boron reagents, stoichiometric silver salts are necessary to activate the donor. Organocatalytic 15 formation

Isothioureas, extensively studied as acyl transfer agents, 18 represent an unexplored reagent in glycosylations and were identified as an attractive catalyst scaffold as they are strong Sigma donors.¹⁹ Herein, we disclose the discovery that isothioureas catalyze the formation of both α -1,2-cis glycosides and α -1,2-trans glycosides without the need for special directing groups or functionalization.

We began our investigation with glycosyl bromide 1 and galactose acceptor 2 as our study coupling partners with commercially available tetramisole hydrochloride 3a as the initial catalyst (Table 1). Glycosylation of 1 with 2 formed 4 in moderate yield (64%) but with low selectivity (2:1 α : β) at 10 mol% catalyst loading in toluene at 50 °C in the presence of (iPr)2NEt (Fig. S1, ESI†). Systematic evaluation of reactant stoichiometries, catalyst loading, solvent, concentration, temperature, and choice of acid scavenger identified conditions that furnished 4 in 5:1 $\alpha:\beta$ selectivity in 58% yield. (Fig. S1, ESI†). A panel of other isothioureas was then screened for improved selectivity and yield. While catalyst 3b performed comparably to 3a, we observed that catalysts 3c-3e furnished disaccharide 4 in similar selectivities but in higher yields, suggesting the arene moiety augments reactivity. Catalyst 3f, a [6,5]-containing scaffold led to a lower yield, but with enhanced selectivity $(6:1 \alpha:\beta)$ relative to the [5,5]-scaffold isothiorureas, suggesting the [6,5] motif is important in conveying selectivity. Similarly, catalyst 3g, containing both an arene and the [6,5] scaffold mediated glycosylation with both higher selectivity and yield relative to 3a. Upon screening the commercially available HyperBTM isothioruea (3h) a significant increase in both yield and selectivity was observed, furnishing 4 in 83% yield at 9.5:1 $\alpha:\beta$ selectivity (Table 1). Further investigation showed that ent-HyperBTM (3i) provided 4 in both diminished selectivity and yield, suggesting the specific stereocenters of the phenyl and isopropyl groups within 3h play a crucial role to

of α-linked glycans present an attractive alternative to metalbased methods, with Jacobsen disclosing a bio-inspired approach using anion-binding macrocycles, 16 and Nguyen recently reporting C-2 symmetric phenanthrolines¹⁷ acting on glycosyl bromides as an evolution of pyridine nucleophiles.

^a Department of Chemistry Purdue University, 720 Clinic Drive, West Lafayette, IN 47906, USA. E-mail: aaxelro@purdue.edu

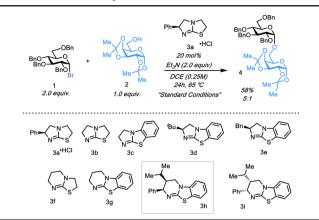
^b Department of Medicinal Chemistry and Molecular Pharmacology Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA

[†] Electronic supplementary information (ESI) available. See DOI: https://doi.org/ 10.1039/d4cc05456c

[‡] These authors contributed equally.

Communication ChemComm

Table 1 Isothiourea catalyst evaluation



Entry	Deviation from standard conditions	Yield, $\alpha\beta$
1	catalyst 3 b	57%, 4.5:1
2	catalyst 3c	67%, 5.2:1
3	catalyst 3d	75%, 5.2:1
4	catalyst 3e	64%, 4.8:1
5	catalyst 3f	55%, 6:1
6	catalyst 3g	71%, 6:1
7	catalyst 3h	83%, 9.5:1
8	catalyst 3i	74%, 4.5:1
9	catalyst 3h, 10 mol%	65%, 10:1

^a All reactions were run at 0.1 mmol scale relative to 2. Yields refer to isolated, purified products, and $(\alpha:\beta)$ ratios were determined by ¹H NMR analysis of unpurified reaction mixtures.

impart selectivity. Lowering the catalyst loading (entry 9, Table 1) of 3h to 10 mol% showed diminished yield, but with similar selectivity to entry 7.

Experimentally, this transformation gives high - to complete α-selectivity and tolerates common sets of protecting groups, including benzyl, benzylidene, silyl, and benzoate groups. While use of chloride donors was found to be competent, reaction times were extended relative to the analogous bromide donors with slightly reduced selectivities (Fig. S3, ESI†). Exposure of 1 to primary alcohol acceptors furnished disaccharides 5 and 6 in good yields, and in good to outstanding alpha selectivity, compared with Lewis-acidic conditions (Fig. 1).20 Notably, in the formation of 6 no aglycone transfer was observed.²¹ Reactions of secondary hydroxyl acceptors, including challenging C-2 and C-3 hydroxyls, occurred in excellent selectivities forming 7 and 8. Glycals, typically coupled through alkylation conditions, 22 reacted smoothly to form 9 with no hydrochlorination by-products. Additionally, 2-deoxy-2-azido sugars are tolerated, forming 10 in good yield, albeit at more modest levels of selection, potentially due to the electronic impact of the azido moiety influencing an S_N1 pathway shift.²³ We then explored benzylidene-protected donors, which can modify conformational plasticity²⁴ of the donor, potentially impacting selectivity. To this end, benzylidene incorporation demonstrated augmented stereoselection, with both primary and secondary hydroxyl acceptors, furnishing disaccharides 11–13 in augmented chemical yields and α-selectivity relative to previous organocatalytic²⁵ approaches and comparable with photoredox strategies, resepectively. 11b Glycosylation with C-6 O-benzoyl and C-6 O-silyl protected donors are tolerated, as

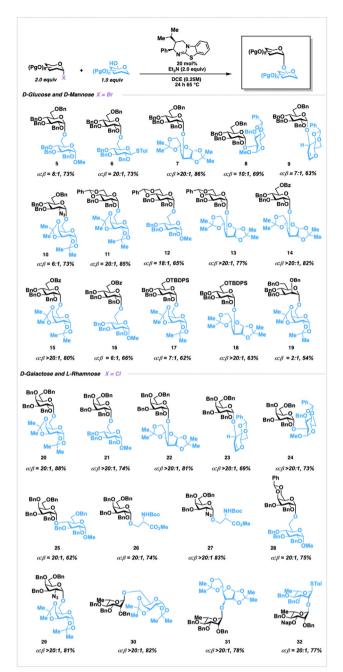


Fig. 1 a Reaction scope. a Reactions run on 0.1 mmol scale relative to acceptor. Yields refer to isolated, purified products, $(\alpha : \beta)$ ratios were determined by ¹H NMR analysis of unpurified reaction mixtures.

evidenced by the formation of 14-16 in both good yields and anomeric ratios. The presence of the sterically demanding C-6 O-TBDPS group attenuated reactivity, as reflected in lower yields of 17 and 18. Interestingly, the formation of 19 occurred with very low selectivity, suggesting that catalyst-glyca conformation is ineffective at promoting selectivity compared to the glucosyl donor-catalyst adducts.

Next, we examined galactosyl donors which were found to react with higher yields (Fig. S3, ESI†), selectivities, and were more stable relative to the bromides.

ChemComm

Disaccharides 20 and 21, for example, were formed with augmented selectivity in comparison to previous reports.²⁵ Glycosylation with secondary acceptors formed the sterically encumbered adducts 22-24 with complete α-selectivity. In addition, disaccharide 25 containing a highly challenging α-1,4 linkage, 26 was obtained in 20:1 α -selectivity. Serine nucleophiles are well tolerated to form O-glycan-type structures²⁷ 26 and. Benzylidene protection of the chloride donor was well tolerated in furnishing 28, and azido disaccharide 29 was prepared in outstanding selectivity. Following this, we explored α-1,2-trans glycoside formation on rhamnoside donors without utilizing the influence of directing or protecting groups for selectivity. Rhamnosylation proceeded through use of the chloride donor and led to the formation of disaccharides 30 and 31 in both good yields and outstanding selectivities from the corresponding primary and secondary hydroxyl acceptors, respectively. Disaccharide 32 was obtained through glycosylation with an unreactive axial O-2 hydroxyl nucleophile. Expanding this reaction to catalystcontrolled oligosaccharide synthesis, we identified 43, a structural component of the Group B Streptococcus agalactiae cell wall as a suitable objective (Fig. 2).28 As oligorhamnans are found in bacterial pathogens, homogeneous access to specific glycoforms could enable investigation into their biological properties and potential as therapeutic targets. Proceeding, glycosylation of acceptor 33 with donor 35, furnished disaccharide 36 in 76% yield as a single α-anomer at gram scale. Removal of the tertbutyldimethylsilyl protecting group with TBAF furnished accep-

Based on literature precedents of amines and heterocycles engaging glycosyl halides to form glycosyl ammoniums, we hypothesize that this reaction proceeds through a double $S_{\rm N}2$ reaction where in the first displacement the catalyst reacts with the glycosyl halide to form an equatorial ammonium species, 17,29 In the second displacement, the glycosyl acceptor reacts to form a new α -linked glycosyl bond and releasing the catalyst

tor 37 in 91% yield, which was then reacted with 35 utilizing

catalyst 3h to provide trisaccharide 38 in 78% yield as a single

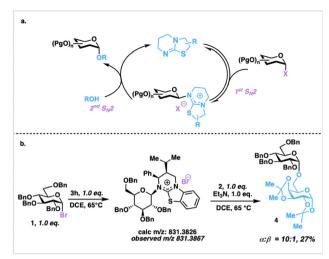
anomer. Following silyl deprotection, and isolation of trisacchar-

ide acceptor 39, glycosylation with 35 generated tetrasaccharide

40 as a single anomer in 70% yield over two steps. Deprotection, followed by glycosylation of **41** with **42**, furnished pentasaccharide

43 as a single anomer in 85% yield over two steps, and confirmed

through both 1D and 2D NMR experiments.



Scheme 1 (a) Proposed reaction mechanism, (b) mass spectrometry study.

(Scheme 1a). We were able to detect this ammonium species through 1 H NMR spectroscopy by reacting **1** with catalyst **3h** and within 1 hour identified two anomeric signals at δ 5.92 ppm and δ 5.73 ppm both in agreement based on previously observed glycosyl ammoniums, 29 and the respective H1–H2 coupling constants are 4.05 Hz and 3.75 Hz, which are smaller than chair and suggestive of a different type of conformation (Fig. S4, ESI†). Additionally, we were able to isolate the catalyst-glycan adduct and characterize it through mass spectrometry, and subsequently react it with **2** to form **4** albeit in modest yield due to the moisture-sensitive adduct (Scheme 1b and Fig. S5, ESI†).

In conclusion, we have identified isothioureas as nucleophilic glycosylation catalysts and specifically the HyperBTM as highly effective for the selective formation of both α -1,2-cis and α -1,2-trans glycosidic linkages. This reaction proceeds without the need for assistance through protecting or directing groups and is operationally direct and mild. It is amenable to both glycosyl chloride and bromide donors with successful application to sterically encumbered linkages and an oligosaccharide. We are currently investigating both the structure of the putative ammonium intermediate, and the overall mechanism through both experimental and computational approaches. Simultaneously, we are currently expanding this platform to other glycan types and more complex oligosaccharides.

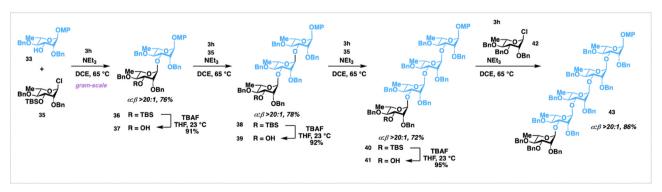


Fig. 2 Synthesis of rhamnan pentasaccharide 42.

Communication ChemComm

B. G., C. E. Z. M. and A. N. W. designed and conducted experiments, and collected and analyzed the data with A. J. A. A. J. A. supervised the research, conceived the project and wrote the manuscript with author input.

This research was supported through generous start-up funding from Purdue University. NIH P30 CA023168 is acknowledged for supporting shared NMR resources to the Purdue Institute for Cancer Research.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) J. Ling and C. S. Bennett, Asian J. Chem., 2019, 8, 802-813; (b) C. J. Crawford and P. H. Seeberger, Chem. Soc. Rev., 2023, 52, 7773-7801.
- (a) M. Liu, X. Qin and X.-S. Ye, Chem. Rec., 2021, 21, 3256-3277; (b) L. Bohé and D. Crich, Carbohydrate Res., 2015, 403, 48-59.
- 3 (a) S. S. Nigudkar and A. V. Demchencko, Chem. Sci., 2015, 6, 3859-3863; (b) Y. Fu, L. Bernasconi and P. Liu, J. Am. Chem. Soc., 2021, 143, 1577-1589; (c) A. Ishiwata, K. Tanaka, J. Ao, F. Ding and Y. Ito, Front. Chem., 2022, DOI: 10.3389/fchem.2022.972429.
- 4 R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, J. Am. Chem. Soc., 1975, 97, 4056-4062.
- 5 R. U. Lemieux and A. R. Morgan, J. Am. Chem. Soc., 1963, 85, 1889-1890.
- 6 A. C. West and C. Schuerch, J. Am. Chem. Soc., 1973, 95, 1333-1335.
- 7 L. Sun, X. Wu, D.-C. Xiong and X.-S. Ye, Angew. Chem., Int. Ed., 2016, 55, 8041-8044.
- (a) T. J. Boltje, J.-H. Kim and G.-J. Boons, Nat. Chem., 2010, 2, 552–557; (b) R. A. Mensink and T. J. Boltje, Chem. Eur. J., 2017, 23, 17637–17653.
- (a) J. P. Yasomanee and A. V. Demchenko, Angew. Chem., Int. Ed., 2014, 53, 10453-10456; (b) X. Liu, Y. Song, A. Liu, Y. Zhou, Q. Zhu, Y. Lin, H. Sun, K. Zhu, W. Liu, N. Ding, W. Xie, H. Sun, B. Yu, P. Xu and W. Li, Angew. Chem., Int. Ed., 2022, 61, e202201510; (c) J. T. Walk, Z. A. Buchan and J. Montgomery, Chem. Sci., 2015, 6, 3448-3453.
- (a) Y. Kobayashi and T. Mukaiyama, Bull. Chem. Soc. Jpn., 2005, 78, 910-916; (b) S. K. Mulani, W.-C. Hung, A. B. Ingle, K.-S. Shiau and

- K.-K. T. Mong, Org. Biomol. Chem., 2014, 12, 1184-1197; (c) L. Wang, H. S. Overkleeft, G. A. Van Der Marel and J. D. C. Codée, J. Am. Chem. Soc., 2018, 140, 4632-4638; (d) J. Park, S. Kawatkar, J.-H. Kim and G.-J. Boons, Org. Lett., 2007, 9, 1959-1962.
- 11 (a) Y. Feng, T. Guo, H. Yang, G. Liu, Q. Zhang, S. Zhang and Y. Chai, Org. Lett., 2022, 24, 6282-6287; (b) C. Zhang, H. Zuo, G. Y. Lee, Y. Zou, Q.-D. Dang, K. N. Houk and D. Niu, Nat. Chem., 2022, 14, 686-694; (c) S. Zhou, X. Zhong, A. Guo, Q. Xiao, J. Ao, W. Zhu, H. Cai, A. Ishiwata, Y. Ito, X.-W. Liu and F. Ding, Org. Lett., 2021, 23, 6841-6845.
- 12 X. Ma, Z. Zheng, Y. Fu, X. Zhu, P. Liu and L. A. Zhang, J. Am. Chem. Soc., 2021, 143, 11908-11913.
- 13 M. Tanaka, A. Nakagawa, N. Nishi, K. Iijima, R. Sawa, D. Takahashi and K. Toshima, J. Am. Chem. Soc., 2018, 140, 3644-3651.
- 14 K. A. D'Angelo and M. S. Taylor, J. Am. Chem. Soc., 2016, 138, 11058-11066.
- 15 M. M. Nielsen, T. Holmstrøm and C. M. Pedersen, Angew. Chem., Int. Ed., 2021, **61**, e202115394.
- 16 Y. Park, K. C. Harper, N. Kuhl, E. E. Kwan, R. Y. Liu and E. N. Jacobsen, Science, 2017, 355, 162-166.
- 17 F. Yu, J. Li, P. M. DeMent, Y.-J. Tu, H. B. Schlegel and H. M. Nguyen, Angew. Chem., Int. Ed., 2019, 58, 6957-6961.
- 18 (a) V. B. Birman and X. Li, Org. Lett., 2006, 8, 1351-1354; (b) G. Xiao, G. A. Cintron-Rosado, D. A. Glazer, B.-M. Xi, C. Liu, P. Liu and W. Tang, J. Am. Chem. Soc., 2017, 139, 4346-4349; (c) J. E. Taylor, S. D. Bull and J. M. J. Williams, Chem. Soc. Rev., 2012, 41, 2109-2121; (d) A. J. Nimmo, J. Bitai, C. M. Young, C. McLaughlin, A. M. Z. Slawin, D. B. Cordes and A. D. Smith, Chem. Sci., 2023, 14, 7537-7544.
- 19 B. Maji, C. Joannesse, T. A. Nigst, A. D. Smith and H. Mayr, J. Org. Chem., 2011, 76, 5104-5112.
- 20 S. S. Nigudkar, K. J. Stine and A. V. Demchenko, J. Am. Chem. Soc., 2014, 140, 11942-11953.
- 21 Z. Li and J. C. Gildersleeve, J. Am. Chem. Soc., 2006, 128, 11612-11619.
- 22 P. H. Seeberger, M. Eckhardt, C. E. Gutteridge and S. J. Danishefsky, J. Am. Chem. Soc., 1997, 119, 10064-10072.
- 23 P. R. Andreana and D. Crich, ACS Cent. Sci., 2021, 7, 1454-1462.
- 24 (a) D. Crich and L. Li, J. Org. Chem., 2007, 72, 1681–1690; (b) R. A. Jeanneret, S. E. Johnson and M. C. Galan, J. Org. Chem., 2020, 85, 15801-15826.
- 25 M. Shaw, Y. Kumar, R. Thakur and A. Kumar, Beilstein J. Org. Chem., 2017, 13, 2385-2395.
- 26 F. Yu, J. L. Dickson, R. S. Loka, H. Xu, R. N. Schaugaard, H. B. Schlegel, L. Luo and H. M. Nguyen, ACS Catal., 2020, 10, 5990-6001.
- (a) D. M. Beckwith and M. Cudic, Sem. Immunol., 2020, 47, 101389; (b) S. D. Kuduk, J. B. Schwarz, X.-T. Chen, P. W. Glunz, D. Sames, G. Ragupathi, P. O. Livingston and S. J. Danishefsky, J. Am. Chem. Soc., 1998, 120, 12474-12485.
- 28 H. Guérin, S. Kulakauskas and M.-P. Chapot-Chartier, J. Biol. Chem., 2022, 298, 102488-102504.
- 29 R. U. Lemieux and A. R. Morgan, Can. J. Chem., 1965, 43, 2205-2213.