ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

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

Received 14th October 2024,
Accepted 6th January 2025

DOI: 10.1039/d4cc05456c

rsc.li/chemcomm

Isothiourea – catalyzed α-selective glycosylations†

Bhaswati Ghosh,‡[a] Charles Enlow,‡[a] Zhichen Ma,[a] Ashley N. Warden[a] and Abram J. Axelrod *[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.[1] 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,[4] pyridine,[5] amine,[6] and phosphine[7] 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 main-group 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 of α-linked glycans present an attractive alternative to metal-based methods, with Jacobsen disclosing a bio-inspired approach using anion-binding macrocycles,[16] and Nguyen recently reporting C-2 symmetric phenanthrolines[17] acting on glycosyl bromides as an evolution of pyridine nucleophiles.

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.

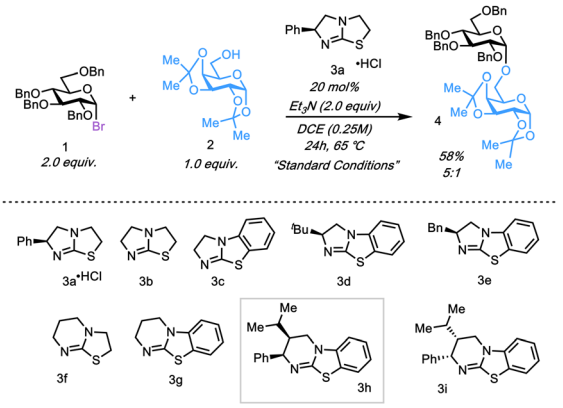
We began our investigation with glycosyl bromide **1** and galactose acceptor **2** as our study coupling partners with commercially available tetramisole hydrochloride **3a** as the initial catalyst (Table 1). Glycosylation of **1** with **2** formed **4** in moderate yield (64%) but with low selectivity (2 : 1 $\alpha:\beta$) at 10 mol% catalyst loading in toluene at 50 °C in the presence of $(^{i}Pr)_2NEt$ (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

[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.

Table 1 Isothiourea catalyst evaluation[a]



Entry	Deviation from standard conditions	Yield, $\alpha\beta$
1	catalyst **3b**	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 (α : β) ratios were determined by ^{1}H 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 plasticity[24] 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 organocatalytic[25] approaches and comparable with photoredox strategies, resepectively.[11b] Glycosylation with C-6 *O*-benzoyl and C-6 *O*-silyl protected donors are tolerated, as

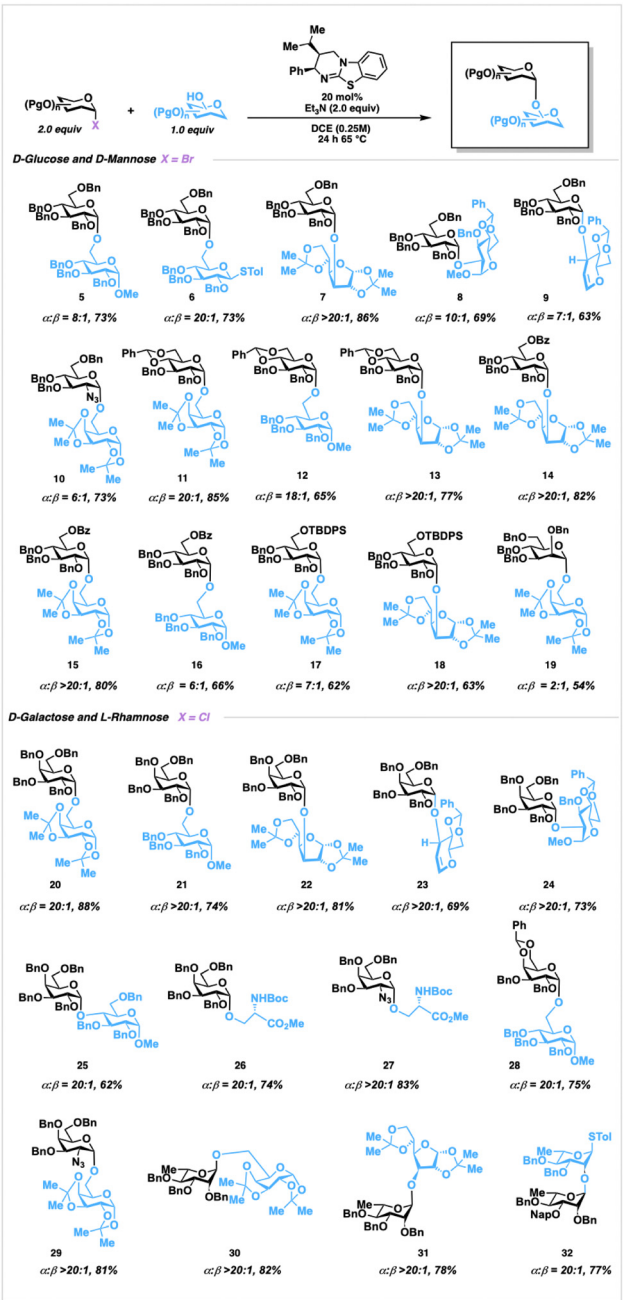


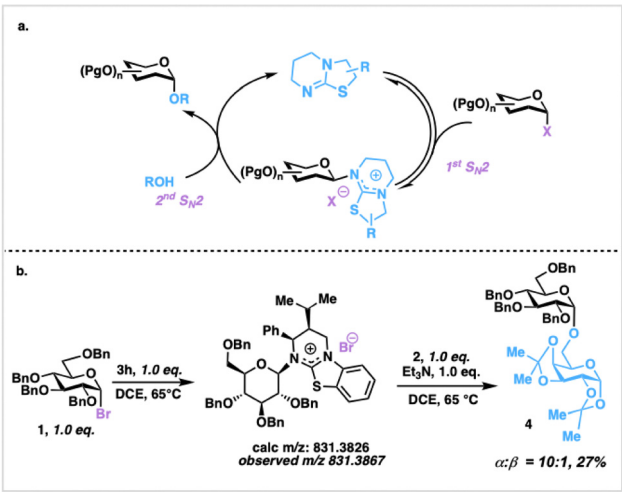
Fig. 1 [a] Reaction scope. [a] Reactions run on 0.1 mmol scale relative to acceptor. Yields refer to isolated, purified products, (α : β) ratios were determined by ^{1}H NMR analysis of unpurified reaction mixtures.

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.

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 structures[27] **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 catalyst-controlled oligosaccharide synthesis, we identified **43**, a structural component of the 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 *tert*-butyldimethylsilyl protecting group with TBAF furnished acceptor **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 trisaccharide 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.

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_N2 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



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 δ5.92 ppm and δ5.73 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.

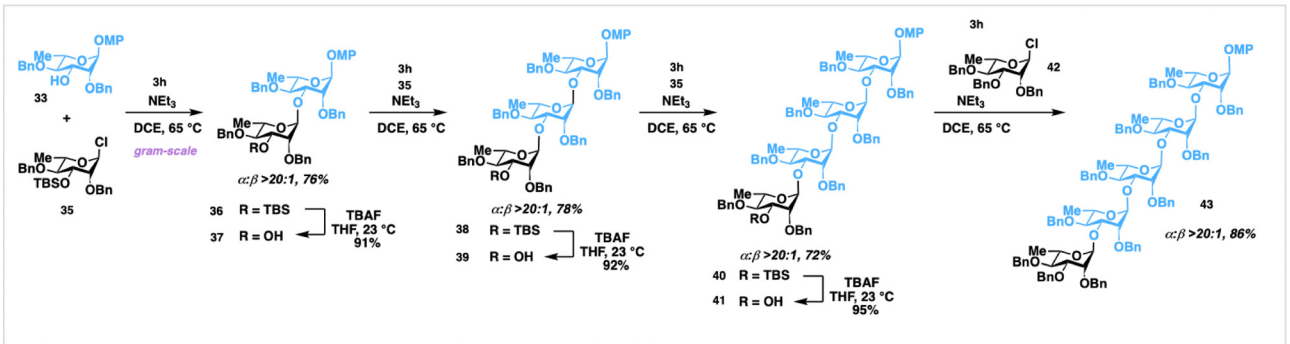


Fig. 2 Synthesis of rhamnan pentasaccharide **42**.

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.
2 (*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.
8 (*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.
9 (*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.
10 (*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.
27 (*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.