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An S_N2-Type Strategy toward 1,2-*cis*-Furanosides

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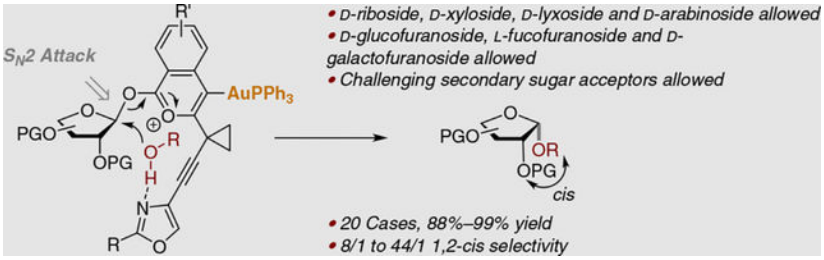
Abstract

The stereoselective construction of 1,2-*cis* furanosidic linkage is synthetically challenging. A strategy that applies to all furanose types remains elusive. In this work, a solution is developed based on gold catalysis and the deployment of the directing-group-on-leaving-group strategy, where a basic oxazole group in the gold-activated leaving group facilitates the stereoinvertive attack by glycosyl acceptors. In addition to exhibiting good to excellent 1,2-*cis* selectivities, these furanosylation reactions are high-yielding and mostly complete in 30 min to 2 h. A broad range of 1,2-*cis*-furanosides is prepared. Although some are uncommon, the ease of access enabled by this approach presents new opportunities to study their applications in medicine and materials research.

Graphical Abstract



Keywords

gold catalysis; stereoselective glycosylation; 1,2-*cis*-furanosides; furanosylation; S_N2

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[†] X. Ma and Y. Zhang contributed equally to this work.

Conflict of Interest
The authors declare no competing financial interest.

Supporting Information
Supporting Information is available and includes experimental procedures and NMR spectra.

Introduction

Existing in various oligo- and polyfuranosides found in many bacteria, fungi, plants, and parasites (see Figure 1a for examples),[1–4] the 1,2-cis-furanosidic linkages are synthetically challenging.[5–8] In comparison to 1,2-*cis*-pyranosidic linkages, the added difficulties in the synthesis of 1,2-*cis*-furanosides stem from the ease of forming furanosyl oxocarbenium intermediates and the ring conformational flexibility (Figure 1b).[9,10] Innovative approaches to addressing these challenges have been developed and include catalysis by *bis*-thiourea hydrogen bond donors,[11] intramolecular aglycon delivery,[12] the use of conformationally restricted donors,[8,13,14] hydrogen-bond-mediated aglycone delivery using functionalized *O*-protecting groups,[15,16] and more recently phenanthro-line-mediated 1,2-*cis* furanosylations.[17] However, a general synthetic strategy applicable to a broad range of furanose donors and a variety of saccharide acceptors is yet to be developed.

Recently, we developed an S_N2-type strategy for stereoselective construction of 1,2-*cis*-pyranosidic linkage.[18] As shown in Scheme 1a, the donor is a glycosyl 4,5-dimethoxybenzoate featuring an oxazole-functionalized cyclopropyldialkynyl group substituted at the benzene ring C2 position. Upon the $IMesAu^+$-promoted cyclization, which was initially reported by Asao et al.[19] and later creatively applied in carbohydrate chemistry by Yu et al.,[20,21] the donor benzoate moiety is converted into the substantially more nucleofugal isochromenylium moiety in the intermediate **A.** In this intermediate, the mildly basic oxazole is engineered to be suitably positioned to form H-bond with an alcoholic acceptor and hence direct its attack at the anomeric center from the backend of the anomeric carbon-leaving group (LG) bond, thereby achieving the desired S_N2-type glycosylation. As the oxazole-directing group is part of the LG, the design, which we term directing-group-on-leaving-group (DGLG), is not limited to a particular sugar type and could offer needed general applicability in glycosylation. This pyranosylation chemistry, however, has difficulty in forming 1,2-*trans* glycosides from 1,2-*cis* donors and typically requires long reaction times (≥16 h). In this work, we demonstrate that the S_N2-type approach operates surprisingly well in the more challenging furanoside synthesis and permits high-yielding and highly stereoselective construction of a broad range of 1,2-*cis*-furanosidic linkages from 1,2-*trans*-furanosyl donors in <2 h (Scheme 1b). Moreover, in the cases of xyloside and riboside, stereoinversion of either anomeric donor is realized, which offers direct evidence of an S_N2 mechanism and was not observed in our pyranosylation chemistry.[18] Although some of the 1,2-*cis*-furanosides are uncommon, the ease of access enabled by this approach opens up new opportunities to study their applications in medicine and materials research.

Although Yu et al.'s[20,21] glycosyl *ortho*-alkynylbenzoate approach, which lacks the oxazole-directing group, features mild conditions and exhibits high efficiency in the synthesis of pyranose-based oligo/polysaccharides and glycoconjugates,[22–24] its applications toward furanoside synthesis are mostly limited to *N*-furanosylation.[25,26] The only *O*-furanosylations[27,28] are reported as single cases in the synthesis of glycosylated natural products. All of these studies employ disarmed donors to construct 1,2-*trans*-furanosidic linkages[25,27,28] and 1,3-*trans*-2-deoxyfuranosidic linkages[26] via neighboring and long-distance acyl group participation, respectively. To date, no stereoselective construction of 1,2-*cis*-furanosides has been studied by this *ortho*-alkynylbenzoate approach. To this end,

we decided to also examine the related donors of each furanoside type without the oxazole-directing group to offer a comparative evaluation of the utility of the DGLG strategy in furanosylation.

The 1,2-*trans*-furanoside donors employed in this study were prepared in two robust and straightforward steps, that is, *N,N'*-dicyclohexylcarbodiimide-mediated esterification between an armed reducing sugar and the 2-iodobenzoic acid and the Sonogashira coupling (see Scheme 1b and Supporting Information Table S1 for details). The esterification step favors the desired 1,2-*trans* configuration for every studied sugar type, with selectivity over 1,2-*cis* configuration ranging from 4:1 in the case of xylose to 1,2-*trans* only in the cases of ribose and lyxose. Pure 1,2-*trans* O-iodobenzoate intermediates were obtained either via column chromatography or recrystallization in 65%–90% yield. The Sonogashira reactions were efficient, with yield typically higher than 78% and in some cases up to 98%. For 1,2-*cis* furanoside donors, alternative esterification strategies (e.g., using benzoyl chloride) were employed to increase its formation, and the donors of xylose and ribose were isolated pure upon column chromatography. Besides the ease of accessing these donors in their pure forms, they are bench-stable and do not undergo appreciable decomposition at ambient temperature in a couple of months. Notably, in the reported S_N2 furanoylation approaches,[11] there are difficulties in preparing anomerically pure donors, which inevitably affects the product anomeric selectivity.

Results and Discussion

The reactions of xylofuranosyl donors

At the outset, we chose to study the synthesis of *D*-xylofuranosides and in particular the α-anomers,[14] which do not succumb to the previously reported bis-urea-catalyzed S_N2-type approach.[11] Seven xylosyl donors, that is, the α- and β-anomers of **D1–D3** and β-**D4**, were prepared. Pure α-**D4** could not be prepared and hence was not examined. As shown in the graph underneath Table 1, **D1** possesses the optimized oxazole-functionalized 3,4-dimethoxybenzoate moiety along with 4-tert-butylbenzyl (PTB) as the *O*-protecting group, which serves the purpose of improving the donor's solubility in nonpolar solvents. Compared to **D1**, **D2** lacks the oxazole-directing group, **D4** lacks the benzene-ring methoxy groups, and **D3** lacks both. In the cases of **D3** and **D4**, the absence of electron-donating MeO groups should enhance the nucleofugality of the gold-activated LGs. As such, the glycosylation reaction may experience increased S_N1 characteristics. In addition, the *O*-protecting groups in **D3** are benzyl groups. These donors reacted with methyl 2,3,4-tri-*O*-benzyl-α-*D*-glycopyranoside (i.e., **2a**), and the results are shown in Table 1. Under the shown reaction conditions with the prototypical and shelf-stable Gagosz complex $Ph_3PAuNTf_2$ as the catalyst,[29] the reaction of β-**D1** exhibited a high level of stereoinversion, affording the α-xylofuranoside α-**3a** featuring a 1,2-*cis*-glycosidic linkage in nearly quantitative yield and with a ratio of 16.2:1 over its β-anomer (entry 1). Moreover, the reaction went to completion in 1 h. In comparison, the reaction of β-**D2** was slower and exhibited a lower α/β selectivity of 7.5/1 (entry 2), confirming the expected beneficial directing effect of the oxazole ring in both the α-selectivity and the reaction rate. Moreover, replacing all of the *O*-PTB groups of β-**D2** with *O*-Bn groups had little impact on the

glycosylation stereoselectivity (see Supporting Information Table S2). Interestingly, little difference between β-**D3** and β-**D4** was detected in their reactions with **2a** (entries 3 and 4). The lack of apparent directing effect here suggests that the bonding between the activated LG and the xylofuranosyl moiety is labile in the absence of the benzene-ring MeO groups, and the reaction hence experiences more S_N1 characteristics. These results reveal the importance of the MeO groups, in the case of β-**D1** in making the gold-activated LG less nucleofugal and hence being more prone to the directing-group-promoted S_N2-type attack. On the other hand, the results with **D2** and **D3** reveal that Yu's system, despite not having been previously reported with armed donors, exhibits moderate S_N2 characteristics.[30] When the reaction solvent was switched from $PhCF_3$/cyclohexane (*v*/*v* = 4:1) to DCM, the α-selectivities were consistently lower (entries 5–7). To rule out that these observed α-selectivities are not inherent to the oxocarbenium intermediate in an S_N1 pathway, we studied the reactions of the α-donors under identical optimal reaction conditions. Much to our delight, in all three cases (entries 8–10), configuration inversion at the anomeric position predominated. Moreover, the reaction of α-**D1** led to the best ratio of 10/1, favoring the β-xylofuranoside β-**3a**. These results support a predominant S_N2 pathway in the reaction of either of the **D1** anomers (entries 1 and 8).

We then briefly explored the scope of this xylofuranosylation chemistry using representative acceptors. As shown in Figure 2, with the more reactive acetonideprotected galactoside acceptor (**2d**, vide infra), the reaction of both β-**D1** and α-**D1** exhibited excellent efficiency and a higher level of stereoinversion than that with **2a**, leading to the formation of either of the **3d** anomers with ≥24/1 selectivity. Gratifyingly, the reaction of β-**D1** with the sterically hindered glucose-derived secondary alcohol acceptor **2b** (vide infra) remained highly stereoinvertive at a lower temperature (i.e., −25 °C), affording the 1,2-*cis*-xylofuranoside α-**3b** in 97% yield. On the other hand, the reaction of α-**D1** with this challenging acceptor was surprisingly slow and not stereoselective (Supporting Information Figure S1). Inspection of the crude NMR revealed some epimerization at the anomeric position, that is, the formation of β-**D1** (Supporting Information Figure S2). The donor epimerization explains the lack of stereoselectivity, and the related phenomena in both furanoside[5] and pyranoside[31] chemistry were previously known.

The reaction scope with other furanosyl donors

We subsequently turned our attention to applying the gold catalysis to the synthesis of the other three types of D-pentofuranosides by using the donors shown in Figure 3a. We limited the acceptors to the glucosides **2a** and **2b** (see Figure 3c), the latter of which, as revealed above, exhibits low nucleophilicity due largely to steric hindrance and is considered a challenging acceptor in carbohydrate synthesis. The reactivity range outlined by these two representative acceptors should provide valuable guidance when other acceptors are considered.

In the case of D-arabinose (Figure 4a), the glycosylation of **2a** by α-**D5** possessing the oxazole-directing group afforded the product β-**4a** with a ratio of 16:1 favoring the 1,2-*cis*-glycosidic linkage. The reaction was also fast and high-yielding. In comparison, without the directing group, the donor α-**D6** led to a moderate β/α ratio of 6:1, confirming the directing

effect in the reaction of α-**D5**. With the more hindered **2b** as the acceptor, by lowering the reaction temperature to −25 °C, the β/α selectivity was 8/1 with excellent yield. Again, the reaction with donor α-**D5** showed substantial enhancement in selectivity compared to that with donor α-**D6** under the same conditions (i.e., −15 °C). In the case of D-lyxose (Figure 4b), the furanosylation of **2a** with the α-donor featuring the oxazole-directing group, that is, α-**D7**, was highly β-selective, despite all four ring substituents in the furanoside β-**5a** being on the same side, and the yield was 93%. Without the directing group in α-**D8**, the β/α selectivity was notably lower, that is, 13/1 instead of 22/1, again revealing the usefulness of the directing strategy. Similar results were obtained in the cases of the furanoside acceptors **2c** and **2e** (see Figure 3c), and the difuranosides β-**5c** and β-**5e** were formed in high yields and with excellent stereoselectivities. With sterically hindered **2b** as the acceptor, both α-donors afforded the 1,2-*cis*-lyxoside β-5b with moderate selectivities. It is noteworthy that the previous S_N2 approaches are either not suited for the 1,2-*cis*-lyxoside construction[11] or exhibit low stereoselectivity.[17] This largely S_N2 approach to these 1,2-*cis*-β-furanosides is remarkable.

In the formation of 1,2-*cis*-ribosides (Figure 4c), we discovered that the directing group does not afford improved selectivity. For example, the furanosylation of **2a** with either β-donor, that is, β-**D9** or β-**D10**, led to a similarly high level of α-preference. The same phenomenon was observed in the reaction of the more challenging **2b**. In this case, the α/β ratios are 17~18/1. With the α-anomers of **D9** and **D10** available in pure form, their reactions with **2a** were less stereoinvertive than the β-counterparts. However, the directing group offers notable benefit in this case as α-**D9** performed substantially better than α-**D10**. By lowering the reaction temperature to −25 °C, the 1,2-*trans*-ribofuranoside β-**6a** was formed from α-**D9** with an 8/1 selectivity over its α-counterpart and in a combined 95% yield.

The reactions of hexofuranosyl donors

We also examined the reactions of several hexofuranosyl donors (Figure 3b) by focusing on the synthesis of their challenging 1,2-*cis*-furanosidic linkages. As shown in Figure 5a, the D-glucofuranosyl donor β-**D11** reacted with the acceptors **2a** and **2b** smoothly to deliver the stereo-inverted 1,2-*cis*-furanoside products α-**7a** and α-**7b** in ≥92% yields and with 12/1 and 18/1 preference, respectively. The better selectivity in the latter case can be attributed to the increased equivalency of the acceptor **2b** as an α/β ratio of 11:1 was observed with 1.2 equiv of **2b**. This observation is consistent with the anticipated S_N2 characteristics of this glycosylation. The inferior α/β ratio obtained with either acceptor by using directing group-less β-**D12** is again indicative of the beneficial directing effect by the oxazole group in the furanosylation chemistry. The same beneficial impacts of the directing group in stereoinvertive furanosylation were observed with L-fucofuranosyl donors α-**D13** and α-**D14** (Figure 5b). Functionalized with the oxazole directing group, α-**D13** reacted with **2a** and the secondary xylosyl acceptor **2c** (Figure 3c) exceptionally well, affording the β-fucofuranosides **8a** and **8c** in ≥90% yields and with 35/1 and 18/1 β/α selectivities, respectively. In the absence of the directing group, the reactions were substantially less stereoinvertive, with the corresponding β-selectivities being 12/1 and 5.2/1, respectively. In the cases of the D-galactofuranosyl donors β-**D15** and β-**D16**, more pronounced beneficial impacts by the directing group on stereoselectivity were observed. As shown in Figure 5c,

the α/β selectivities were improved by >3 fold in both cases. Moreover, in the case of α-**9d**, the yield (90%) and the selectivity (α/β = 44/1) were improved over those reported via a previous S_N2 approach (78% yield, 11:1).[11]

Conclusion

A general synthesis of challenging 1,2-*cis*-glycosidic linkages in furanoside synthesis is achieved via gold-catalyzed furanosylation. The largely S_N2 nature of the glycosylation is supported by stereoselective conversion of either donor anomer into the configurationally opposing product anomer in the cases of D-xylose and D-ribose. Mostly high levels of stereoinversion at the anomeric position of furanosyl donors are realized by employing the DGLG strategy, in which a basic oxazole moiety is appended to the anomeric LG and directs the backend attack at the anomeric center by a glycosyl acceptor upon gold activation. A broad range of furanoses, including all four D-pentofuranoses, D-glucofuranose, L-fucofuranose, and D-galactofuranose, are suitable donor precursors, and challenging acceptors are accommodated. Except in the case of D-ribose, the direct group strategy offers substantial improvements in reaction S_N2 characteristics among all other explored furanose types. Besides the high selectivities and general applicability toward 1,2-*cis*-furanosides, all the reactions are efficient, with yields routinely >90% and reaction times often between 30 min and 2 h.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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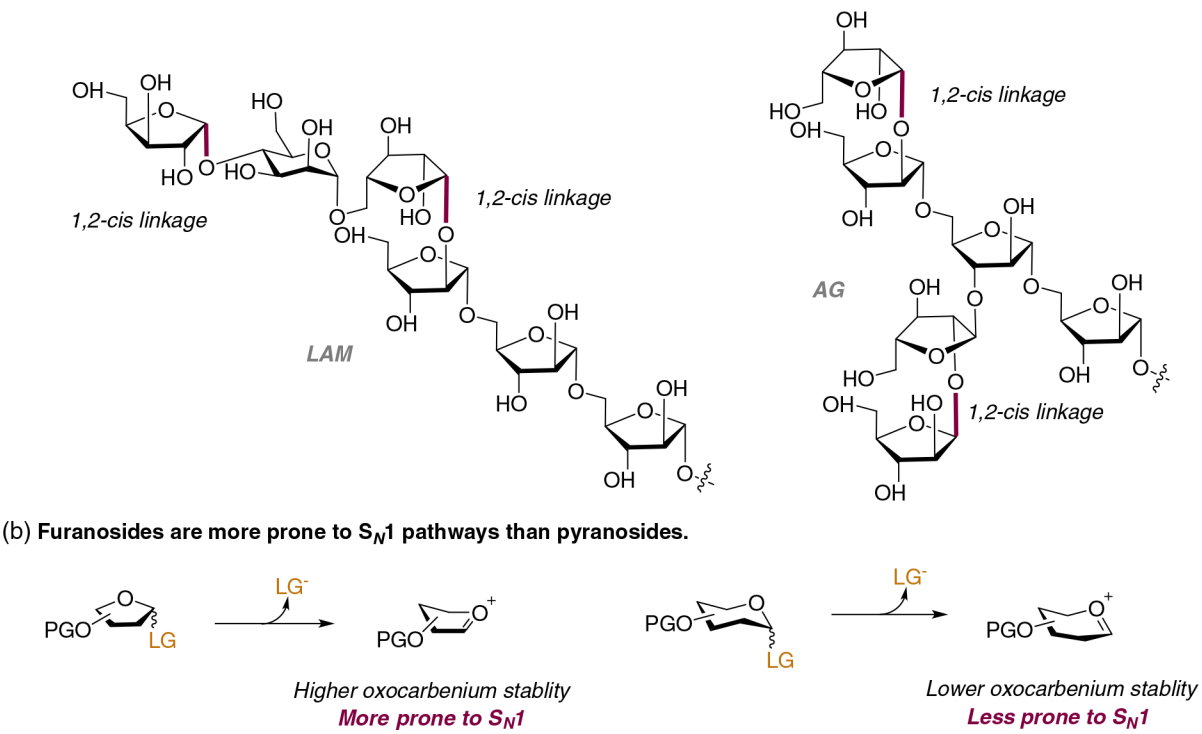
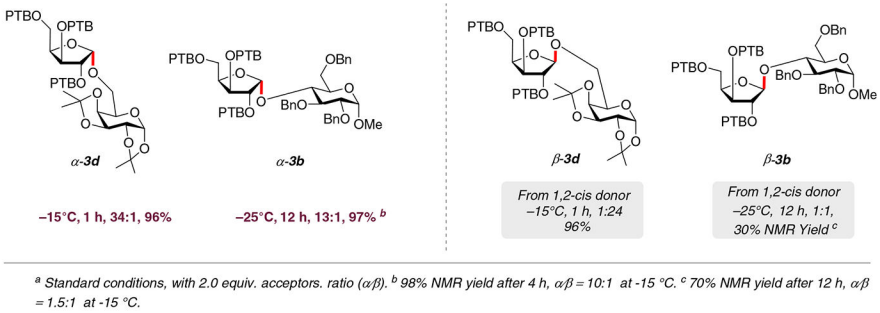


Figure 1 |.

(a) The 1,2-cis furanosidic linkages found in the cell wall hexasaccharide motifs. (b) The reactivity comparison between furanosyl and pyranosyl donors.



[a] Standard conditions, with 2.0 equiv. acceptors. ratio (αβ). [b] 98% NMR yield after 4 h, αβ = 10:1 at -15 °C. [c] 70% NMR yield after 12 h, αβ = 1.5:1 at -15 °C.

Figure 2 |.
The stereoinvertive synthesis of xylofuranosides.

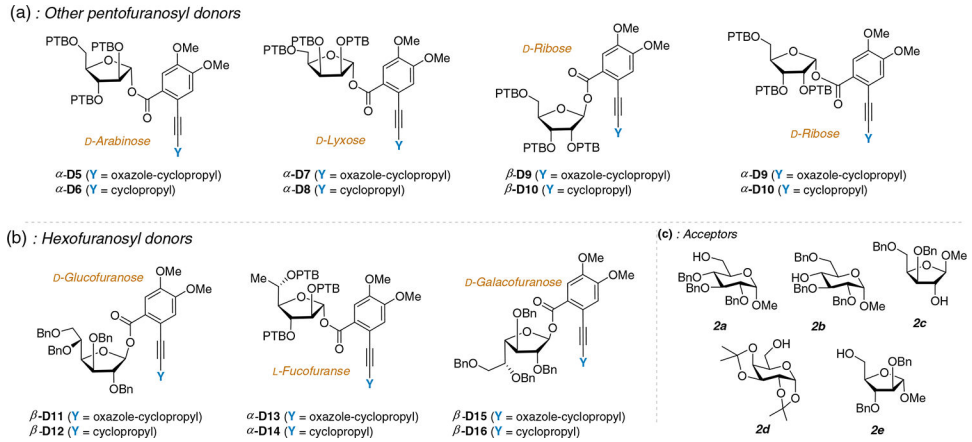


Figure 3 |.
Additional donors and acceptors involved in the scope study.

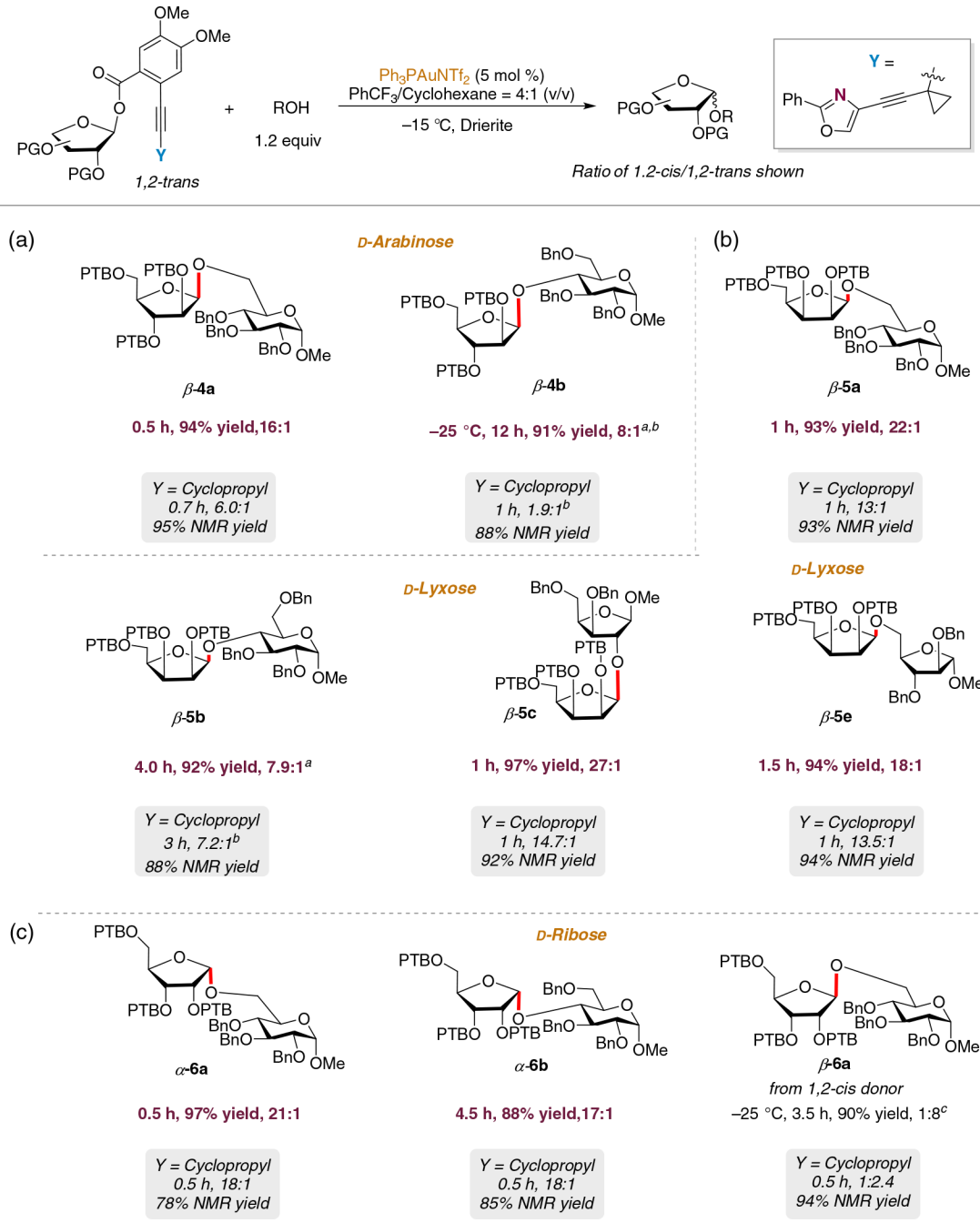
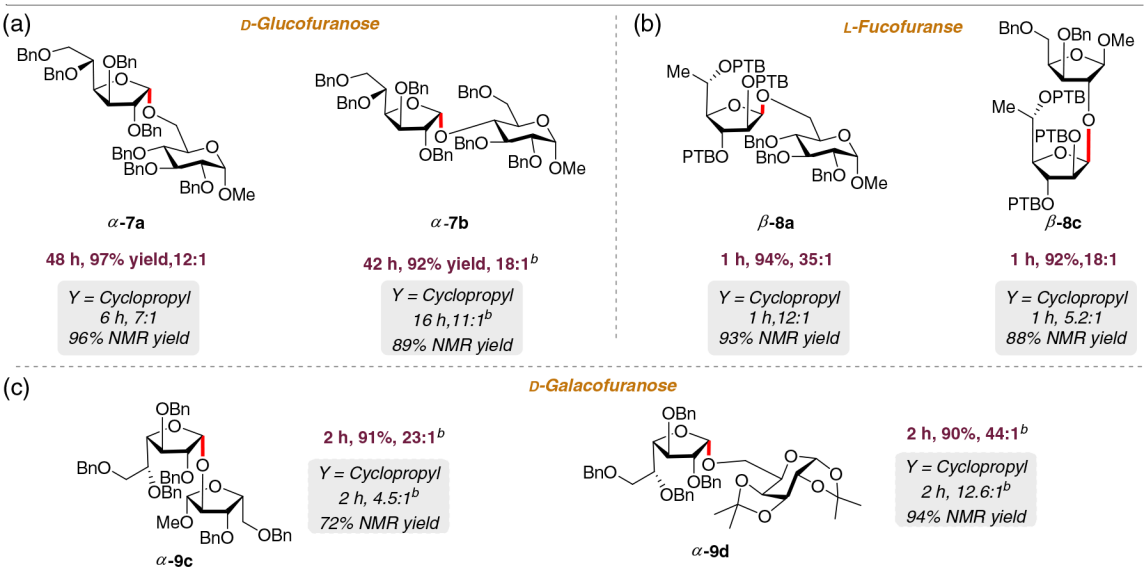


Figure 4 |.

The scope of S_N2-type furanosylation with other pentofuranosyl donors.

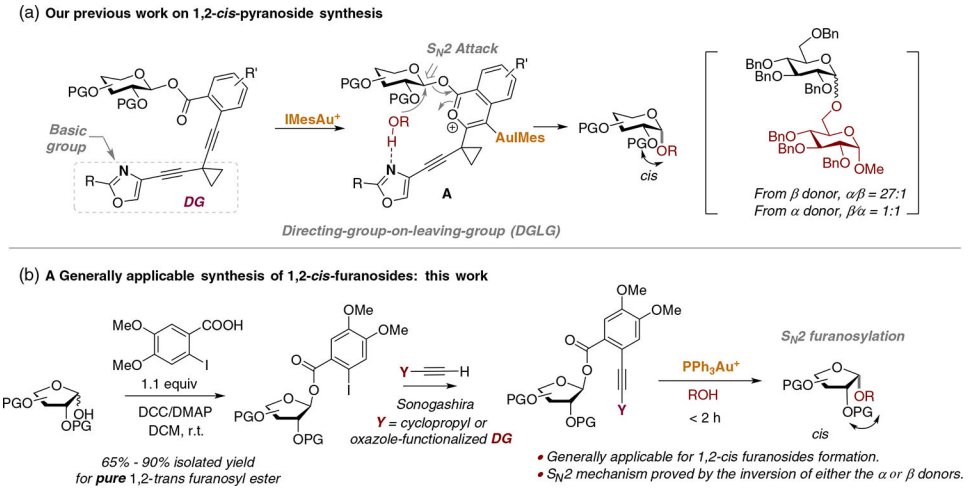
The Reactions of Hexofuranosyl Donors.[a]



[a] *Standard conditions, with 1.2 equiv acceptors.The ratio of 1,2-cis vs 1,2-trans shown.* [b] *With 2.0 equiv acceptors.*

Figure 5 |.

The scope of S_N2-type furanosylation with hexofuranosyl donors.

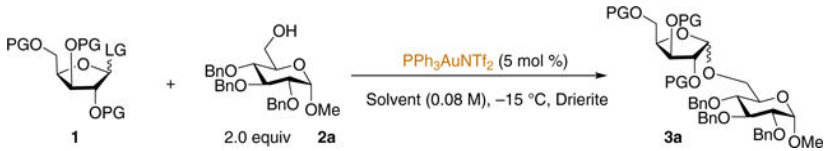


Scheme 1 |.

The DGLG strategy for S_N2-type glycosylation leading to 1,2-cis-glycosidic bonds. DCC = N, N'-dicyclohexylcarbodiimide, DCM = dichloromethane, DMAP = 4-(dimethylamino)pyridine.

Table 1|

The Reactions of Xylofuranosyl Donors



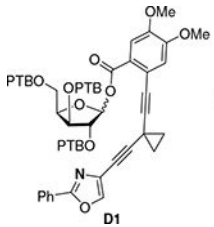
Entry	Donor	Solvent	Time	Conversion	Yield[a]	α/β
1	**β-D1**	**Mixed** [b]	**−15 °C/1 h**	**100%**	**99%**	**16.2:1**[c]
2	**β-D2**	Mixed[b]	−15 °C/1 h	74%	72%	7.5:1
3	**β-D3**	Mixed[b]	−15 °C/0.5 h	100%	99%	8.8:1
4	**β-D4**	Mixed[b]	−15 °C/3 h	100%	98%	9.3:1
5	**β-D1**	DCM	−15 °C/3 h	47%	47%	10.8:1
6	**β-D2**	DCM	−15 °C/1 h	100%	97%	3.0:1
7	**β-D3**	DCM	−15 °C/0.5 h	100%	98%	3.0:1
8	**α-D1**	**Mixed**	**−15 °C/0.5 h**	**100%**	**97%**	**1:10**[d]
9	**α-D2**	Mixed	−15 °C/0.5 h	100%	90%	1:5.5
10	**α-D3**	Mixed	−15 °C/0.5 h	100%	99%	1:6.0

[a] Crude NMR yield.

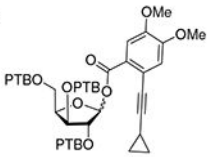
[b] $PhCF_3$/cyclohexane = 4:1 (*v*/*v*).

[c] 97% isolated yield.

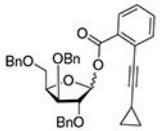
[d] 94% isolated yield.



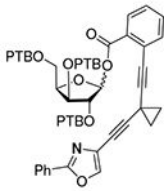
D1



D2



D3



D4