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Halogen-bond-assisted radical activation of glycosyl donors enables mild and stereoconvergent 1,2-*cis*-glycosylation

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The chemistry of carbohydrates has a history of over 100 years, but simple, stereoselective and efficient glycosylation methods remain highly needed to facilitate the studies of sugars in various disciplines. Here we report a strategy for 1,2-*cis*-glycosylation without using metals, strong (Lewis) acids, elaborate catalysts or labile substrates. Our method operates by a unique mechanism: it activates glycosyl donors through a radical cascade rather than the conventional acid-promoted, ionic process. As elucidated by computational and experimental studies, the allyl glycosyl sulfones (as donors) form halogen bond complexes with perfluoroalkyl iodides, which—merely by visible light irradiation—fragment via radical intermediates to give the electrophilic glycosyl iodides. In situ trapping by various nucleophiles affords, in a stereoconvergent manner, the challenging 1,2-*cis*-glycosides. This metal- and acid-free reaction shows remarkable tolerance to functional groups. The high stereoselectivity holds for a broad array of donors. This study suggests that the simple C2-alkoxy group can serve as an effective directing group for building 1,2-*cis*-glycosidic bonds.

Carbohydrates play essential roles in virtually all cellular activities[1,2] (see Fig. 1a for representative examples). Glycosylation reactions[3–7], which install carbohydrate moieties onto target molecules, are thus in high demand in various areas to interrogate and to modulate sugar-mediated biological processes. Since the original work of Michael[8] and Fischer[9], remarkable progress has been made in the construction of glycosidic bonds, and many of the theories established during these investigations have become the cornerstones of modern organic chemistry[10–26]. With the growing appreciation of the importance and utility of carbohydrates[27,28], the quest for efficient glycosylation methods does not fade, but continues to inspire the development of new reagents, strategies and concepts.

A prototypical glycosylation reaction (Fig. 1b) commences by activating the glycosyl donor (**1**) to form a more electrophilic intermediate (for example, a synthetic equivalents of oxocarbenium **3**). Subsequent trapping by a nucleophile (acceptor) affords glycoside **4**, often as a mixture of 1,2-*cis*- and 1,2-*trans*-configured products. Of note, the selective formation of 1,2-*cis*-linkages is more difficult and less developed. Mechanistically, most established strategies activate glycosyl donors via ionic processes, for example, the covalent or coordinative bond formation between the leaving group (X) of **1** and an activating agent (A–B) (Fig. 1b, blue arrow). Some of the most popular glycosylation methods[3–7] that employ glycosyl sulfides, sulfoxides, trichloroacetimidates and *N*-(phenyl)trifluoroacetimidates as donors belong to this class and have remained the mainstay techniques in the field. An intrinsic constraint of this activation mode, however, lies in that it usually employs either a reactive but labile glycosyl donor **1** or a strong and/or harsh activating agent. Use of sensitive substrates and/or reagents may raise functional group compatibility issues and meanwhile cause inconvenience for practitioners. So far, excellent strategies have been established to break such a dilemma, as exemplified by the studies from the Yu group, who employed gold catalysts[20], the Jacobsen group, who employed bis-urea catalysts[22,25], and other groups. Yet, it remains highly desirable to develop general and user-friendly glycosylation methods that avoid sensitive reagents, labile substrates or precious (metal) catalysts. Those that, at the same time, demonstrate high stereoselectivities are more valuable, but elusive.

The development of strategically distinct glycosylation methods is crucial to address some of the intrinsic limitations encountered by the field. Conceivably, glycosyl donor **1** could also be converted into electrophilic intermediate **3** by a two consecutive single-electron transfer steps (Fig. 1b, red arrows). This activation strategy, which is based on a radical–polar crossover[29,30], remains underexplored but may possess great potential due to the exceptional functional-group tolerance of radical processes. Apparently, the application of this strategy is plagued by many obstacles[31–34]: to generate glycosyl radicals **5** often calls for harsh conditions or unstable substrates, and the requirement to oxidize **5** in situ to form **3** poses additional challenges. In the synthesis of *S*-glycosides[35], we recently developed allyl glycosyl sulfones **6** (Fig. 1c) as a class of bench-stable and convenient precursors to glycosyl radicals **5**. We speculated whether we could choreograph the generation of radical **5** from **6** with a mild one-electron oxidation of **5** to access electrophile **3** (or its equivalents), and couple them with a subsequent nucleophilic attack to form *O*- or *N*-glycosidic bonds. Guided by this design, we developed in this work a mild and stereoselective glycosylation method shown in Fig. 1c. In our process, glycosyl donor **6** and C_4F_9I form a halogen-bond (XB) complex **7**, which, on visible light irradiation, fragments through a cascade of single-electron transfer processes to form the glycosyl iodide intermediate **8** via **5**. Subsequent trap by

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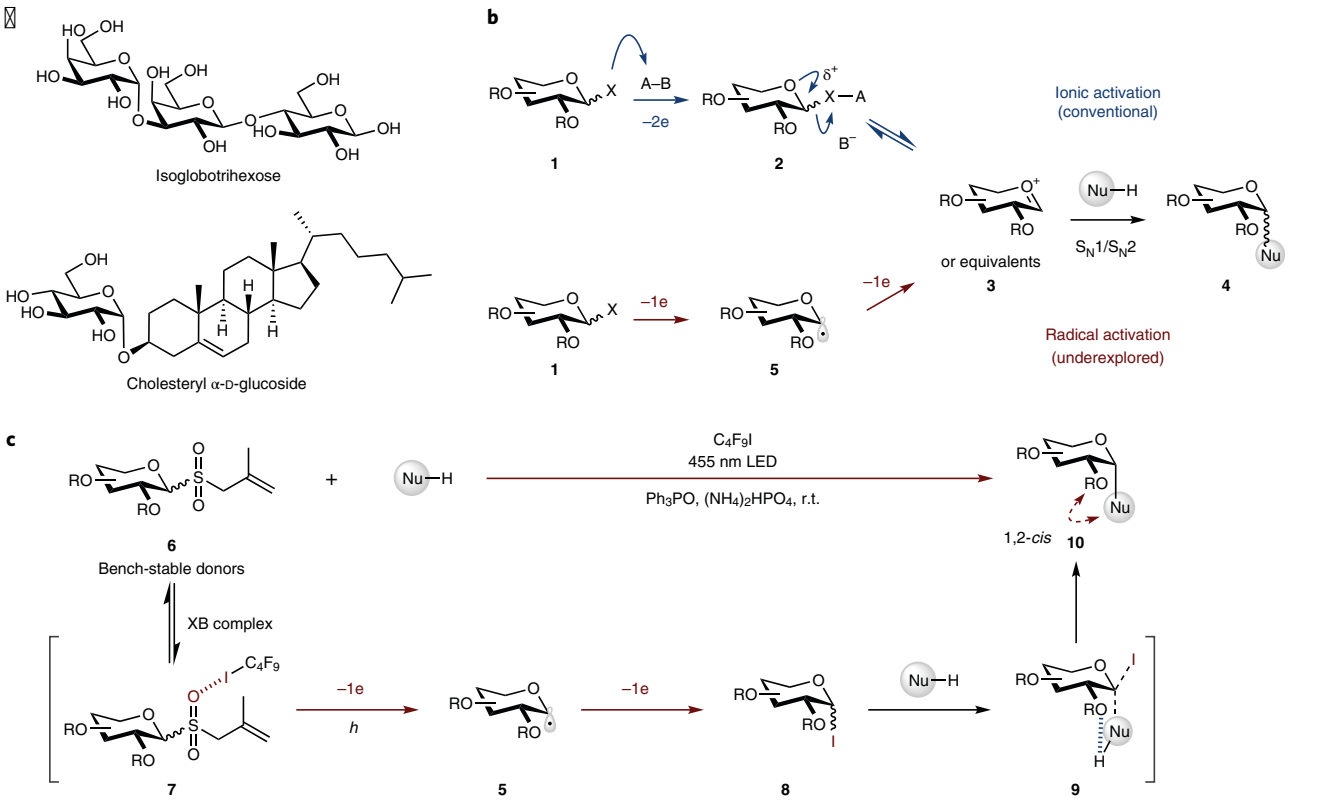


Fig. 1 | Importance of carbohydrates and approaches to build glycosidic bonds. a, Two representative examples of glycosides: isoglobotrihexose, the sugar component of immunomodulatory glycolipid isoglobotrihexosylceramide, and cholesteryl α-D-glucoside, a metabolic product of the cancer-causing pathogen *Helicobacter pylori*. **b**, Two different strategies to make glycosidic bonds. The blue and red arrows indicate the ionic and radical activation of donors, respectively. The radical-based activation strategy remains underdeveloped. **c**, This work: mild and stereoselective glycosylation that features the XB-assisted radical activation of donors. This method, which exploits both XB (**7**) and hydrogen-bond (**9**) interactions, is metal- and acid-free and demonstrates a high generality in making 1,2-*cis*-glycosides. Nu–H, nucleophile; r.t., room temperature; S_N1, unimolecular nucleophilic substitution; S_N2, bimolecular nucleophilic substitution.

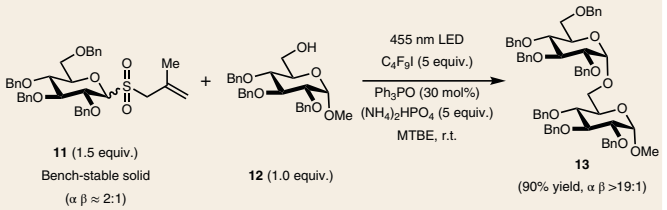
a nucleophile affords glycoside **10** smoothly. Such a radical-based donor-activation strategy (**6** to **7** to **5** to **8**) imparts important advantages to our method. It employs bench-stable donors and avoids harsh activating agents (for example, strong acids, metals or oxidants). It proceeds under metal- and acid-free conditions and accommodates densely functionalized acceptors. Unexpectedly and fortuitously, it is stereoselective and stereoconvergent (**8** to **10** via **9**) and displays a high generality in building 1,2-*cis*-glycosidic bonds, which is another outstanding challenge[36,37] in carbohydrate synthesis. During this study, we found that the C2-alkoxy group in glycosyl donors, often viewed as a non-participating substituent in glycosylation reactions, could serve to direct the formation of 1,2-*cis*-glycosides via hydrogen bonding with acceptors (see **9** in Fig. 1c). Thus, our glycosylation method leverages two types of non-covalent interactions[38,39]: a halogen bond for donor activation and a hydrogen bond for stereochemical control.

Results

Reaction optimization. Our study commenced with the model reaction between sulfone **11** and alcohol **12** (Table 1). After extensive optimization, we found that, when irradiated with a 10 W 455 nm blue light-emitting diode (LED) bulb, **11** and **12** could couple in the presence of C_4F_9I and $(NH_4)_2HPO_4$ to afford disaccharide **13** efficiently (Table 1, entry 1). Allyl glycosyl sulfones[35] are readily available in large quantities (over 10 g prepared per batch) and bench stable. Moreover, each of the other reagents (that is, Ph_3PO, C_4F_9I and $(NH_4)_2HPO_4$) is low cost, bench stable and easy to handle. As another advantage, product **13** was formed with high 1,2-*cis* selectivity, although **11** was employed as a 2:1 diastereomeric mixtures. Control experiments revealed that the use of Ph_3PO was not necessary for product formation but nonetheless helped to slightly enhance the stereoselectivity and yield (Table 1, entry 2, and Fig. 2a)[40,41]. No product formed if C_4F_9I was omitted (entry 3) or substituted with *n*-C_4H_9I (entry 4). In addition, light was essential for the reaction to occur (Table 1, entry 5), but no external photocatalyst was necessary. Although not required, the addition of a photocatalyst does not diminish the reaction efficiency (entry 6). A mild base was required for this transformation (Table 1, entries 7–9). $(NH_4)_2HPO_4$ was chosen for later studies thanks to its low price and mildness. The reaction could proceed in various solvents (Table 1, entries 10 and 11), but the use of acetonitrile dramatically lowered the stereoselectivity. The addition of TEMPO inhibited this reaction completely (entry 12).

Mechanistic studies. To gain a preliminary understanding of the reaction mechanism, we performed the experiments shown in Fig. 2. We prepared sulfone **14**, which bears an allyloxy group at the C2 position. Irradiation of **14** together with C_4F_9I under the above light source afforded cyclized iodide **15** as a product (Fig. 2a). The formation of the C–C bond in **15** implies the intermediacy of glycosyl radical **16**. Moreover, as shown in Fig. 2b, irradiation of **11** with C_4F_9I alone (without any other additives) yielded the known glycosyl iodide **18**, which can be detected by ^{1}H NMR spectroscopy (Supplementary Section 3.3). Substituting **11** with the per-benzoylated **17** allowed us to isolate the corresponding glycosyl iodide **19**. These results suggest that glycosyl iodide **18** is the key intermediate in the

Table 1 | Condition optimization



Entry	Variation from labelled conditions	Yield (%)	α:β
1	None	90[a]	>19:1
2	No Ph_3PO	73	15:1
3	No C_4F_9I	NR	ND
4	C_4H_9I instead of C_4F_9I	NR	ND
5	No light	NR	ND
6	*fac*-Ir(ppy)$_3$ as photocatalyst	89	13:1
7	No $(NH_4)_2HPO_4$	23	11:1
8	K_2CO_3 instead of $(NH_4)_2HPO_4$	88	11:1
9	2,4,6-collidine instead of $(NH_4)_2HPO_4$	89	13:1
10	1,4-dioxane instead of MTBE	80	18:1
11	MeCN instead of MTBE	93	2:1
12	Addition of TEMPO	NR	ND

Reactions were performed on a 0.05 mmol scale at a 0.1 M concentration of **12** for 24 h. Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Diastereomeric ratios were determined by NMR analysis of the crude reaction mixture. [a]Isolated yield at a 0.2 mmol scale. MTBE, methyl *tert*-butyl ether. TEMPO, (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; *fac*-Ir(ppy)$_3$, tris[2-phenylpyridinato-C^2,*N*]iridium(III); NR, no reaction; ND, not determined.

reaction between **11** and **12** to make **13** (Table 1), and this intermediate is generated via a glycosyl radical **20**. It deserves to be mentioned at this stage that glycosyl iodides are among the boldest and most reactive intermediates for glycosylation[40–43]. Systematic studies from the Gervay-Hague and other groups[43] revealed their unique utility in making the challenging 1,2-*cis*-glycosides. However, the difficulties associated with the preparation and manipulation of glycosyl iodides have greatly hampered their application in carbohydrate synthesis. By employing a radical-based activation strategy, our method produces glycosyl iodides under extremely mild and simple conditions. It avoids the use of harsh Lewis acids (for example, trimethylsilyl iodide) and obviates the isolation and handling of the highly reactive intermediates. These advances provide substantial opportunities to explore and exploit the reactivities of glycosyl iodides, and allows access to various glycosides that are difficult to make by conventional approaches (see Tables 2 and 3 for examples).

We were intrigued that our reaction proceeded smoothly in the absence of any typical photocatalysts. We attribute the light-absorbing species to the XB complex formed between sulfone **11** and C_4F_9I, as is supported by the studies of the Yu[44] and the Marian groups[45]. It is well established that electron-deficient iodides (for example, C_4F_9I) bear a σ-hole on the axis of the C–I bond and form halogen bonding with Lewis bases[46]. Indeed, we found that the addition of sulfone **11** to a $CDCl_3$ solution of C_4F_9I caused a noticeable upfield shift of its ^{19}F NMR signals (Fig. 2c). We further deduced from the NMR experiments that sulfone **11** and C_4F_9I form a 1:1 complex, with an association constant (K_a) of 0.91 ± 0.11 (see Supplementary Section 3.4 for details).

We next performed density functional theory calculations (ωB97X-D/def2tzvp/SDD/SMD(Et_2O)//ωB97X-D/6-31G(d)/Lanl2dz/SMD(Et_2O)) to elucidate more details, using sulfone **22** and CF_3I as simplified model substrates (Fig. 2d). We found that XB complex **23** could be formed between the sulfone oxygen of **22** and iodine of CF_3I, with a negative enthalpy of −3.3 kcal mol^{-1}. The O–I distance (3.27 Å) in **23** is 0.23 Å shorter than the sum of their van der Waals radii, and the O–I–C angle is almost linear (178.6°), both consistent with the properties of a XB complex[46]. Further frontier molecular orbital calculations revealed that the XB complex is stabilized by an interaction between the highest occupied molecular orbital of the sulfone and lowest unoccupied molecular orbital of the CF_3I (Supplementary Fig. 4).

Homolytic cleavage of the CF_3–I bond to form the CF_3 radical was calculated to have a free energy barrier of 45.7 kcal mol^{-1}, but this homolysis process is more facile in the XB complex **23** (ΔG = 9.7 kcal mol^{-1}). The CF_3 radical, once generated, adds to the alkene group of **22**, which leads to **Int-I**. Fragmentation[47,48] of **Int-I** releases alkene **25** and sulfur dioxide with low barriers[35] and generates radical **Int-III** (via **Int-II**). Recombination of **Int-III** with the iodine atom produces the key iodide intermediate **Int-IV**, which then serves as a potent alkylating agent (Fig. 2e). It is notable that in recent years the Lewis acidity of XB donors has been exploited to achieve ionic activation of reactive glycosyl donors[49–52] (blue arrow in Fig. 1b). Here, however, we harnessed the XB complex formation to trigger a light-promoted single-electron transfer cascade (red arrow in Fig. 1b), and activated our bench-stable glycosyl donors under very mild conditions.

Substrate scope. The power of our glycosylation reaction is illustrated by its broad scope. A variety of alcohol acceptors could be glycosylated with high stereoselectivities (Table 2). Functional groups, such as cyano (**26a**), nitro (**26b**), terminal alkyne (**26j**), ester (**26f**), ketone (**26ab**) and amide (**26f**) are accommodated. A free indole group is also compatible (**26e**). Acid- and base-sensitive functional groups, such as Fmoc and trityl in **26af**, stayed intact. Sulfides are inert under our conditions (**26v**), which could serve as handles for further glycosylation reactions. Primary, secondary and tertiary alcohols could all be employed. Alcohols derived from serine (**26f**) and threonine (**26o**) underwent the reaction with high efficiencies. Sugar alcohols could be used to yield various disaccharides with high selectivities (**26r**–**26z**). Both primary and secondary hydroxyls in monosaccharide backbones participated in this reaction, and the former displayed a higher reactivity (**26x** and **26z**). Steroidal alcohols are suitable nucleophiles (**26aa** and **26ab**). Although this reaction occurs via a radical mechanism, acceptors that contain radical sensitive functional groups—such as alkenes (**26c** and **26d**), alkynes (**26j**) and weak C–H bonds—are tolerated. Particularly noteworthy is the formation of **26z**, which contains a 2-methylallyl group identical to that in donor **11**. Such selectivities may be attributable to the precomplexation between sulfone donor **11** and C_4F_9I (Fig. 2c,d), which renders the attack of perfluoroalkyl radicals to allyl sulfone pseudo-intramolecular and thus more favoured.

Besides aliphatic alcohols, phenols or carboxylic acids are competent nucleophiles in this reaction (**26ac**–**26af**). For example, the phenolic hydroxyl group in tyrosine derivatives (**26ad**) partook in this reaction smoothly to afford the corresponding 1,2-*cis*-glycosides with good selectivities. No by-product that arises from the *C*-glycosylation of phenols was observed. Highly 1,2-*cis* selective glycosylation of carboxylic acids has been challenging. Our method fills in this gap, as demonstrated in the selective formation of **26ae**, **26af** and **26ak**–**26am**. In addition, nitrogen-based nucleophiles could be glycosylated by our method with high selectivities, as exemplified by the efficient preparation of **26ag** and **26ah**.

We applied this method in the glycosylation of bioactive natural products and commercial drugs. Our method efficiently installed a glycosyl unit onto podophyllotoxin, a potent anticancer agent (**26ai**). The antiviral drug zidovudine could be glycosylated directly under our conditions (**26aj**). The thymidine ring and azide group in this substrate did not interfere with the process. Last, the carboxyl

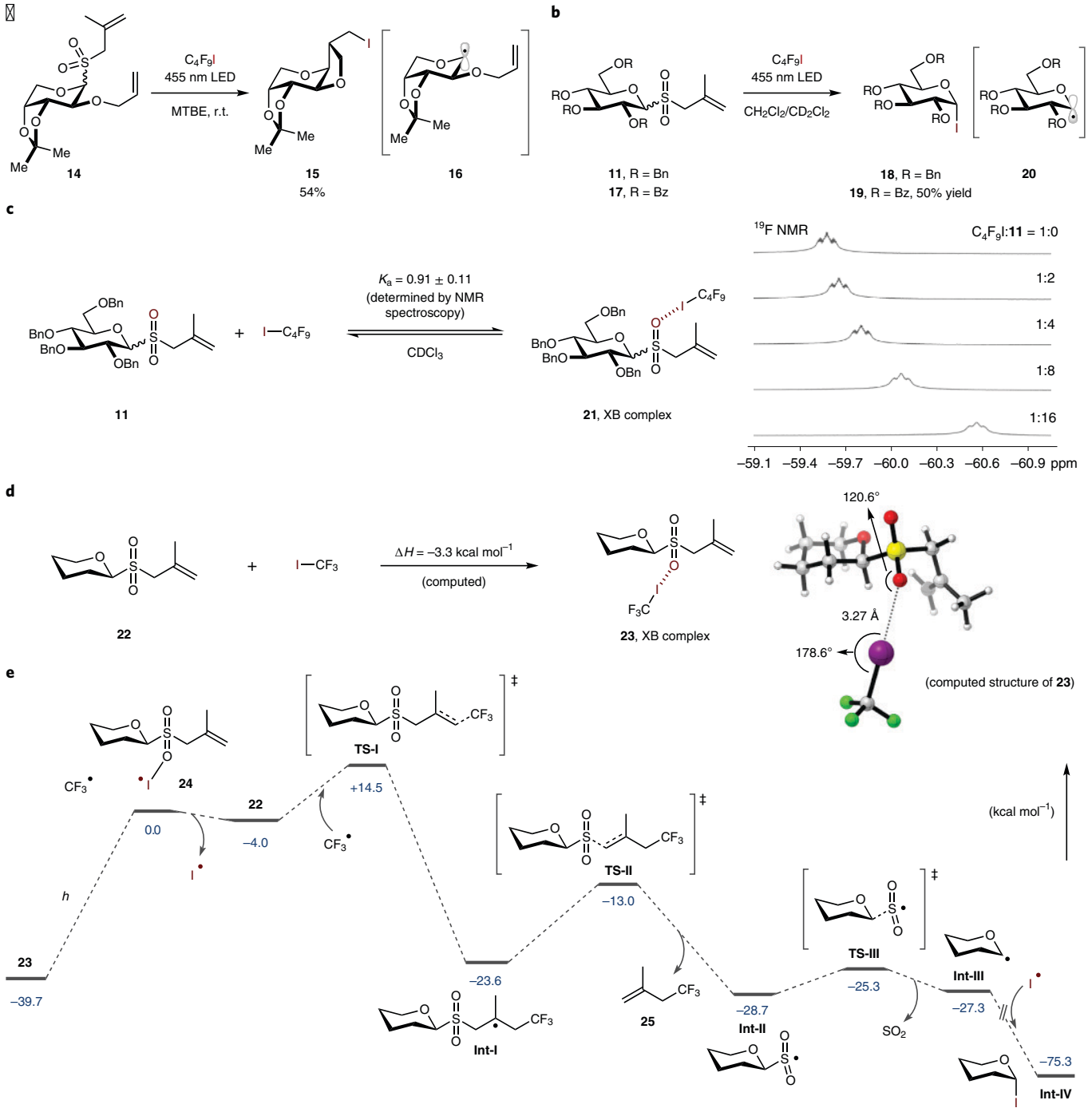
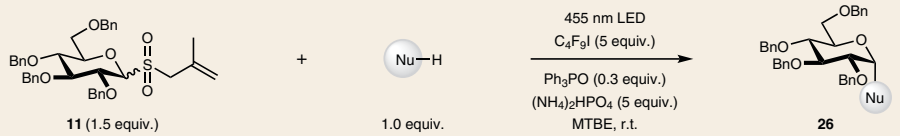


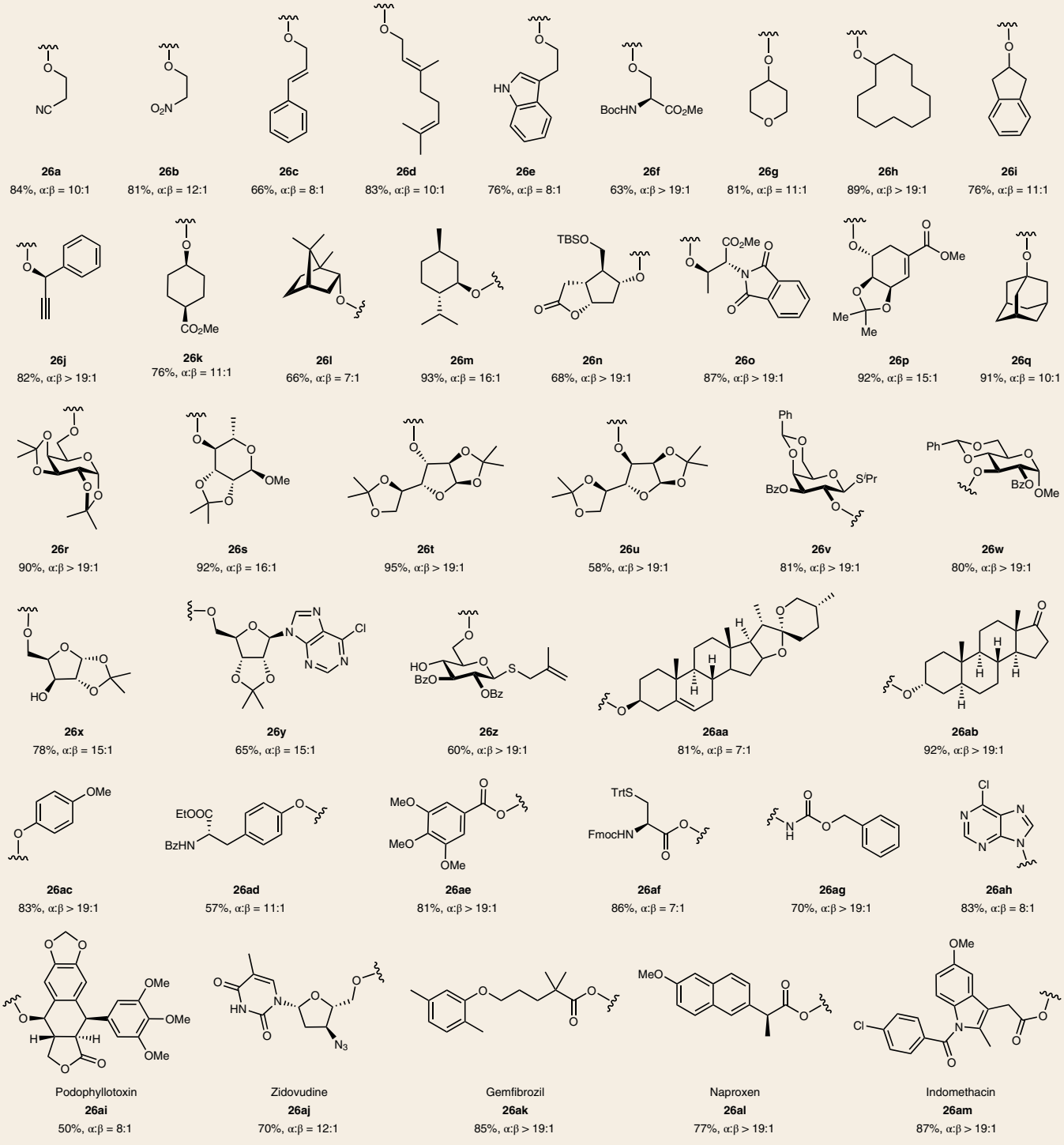
Fig. 2 | Preliminary mechanistic studies. a, Formation of cyclized product **15** supports the intermediacy of **16**. **b**, The formation of glycosyl iodides **18** (detected by NMR spectroscopy) and **19** suggests that glycosyl iodides are key intermediates in our glycosylation reaction. **c**, ^{19}F NMR titration experiments support the formation of XB complex **21**. **d**, Computed structure and energy of XB complex **23**. **e**, Computed donor activation pathway. Complex **23** is photoactivated to homolyse the CF_3–I bond. The resulting $CF_3^{\bullet}$ radical adds to **22**, which then triggers a cascade of bond cleavage steps to generate the key electrophile **Int-IV**, via intermediates **Int-I**, **Int-I** and **Int-III** and transition structures **TS-I**, **TS-II** and **TS-III**. Free energies were computed by ωB97X-D/def2tzvp/SDD/SMD (Et_2O)//ωB97X-D/6-31G(d)/Lanl2dz/SMD (Et_2O).

groups in gemfibrozil, naproxen and indomethacin all functioned as potent acceptors (**26ak**–**26am**).

We next examined the generality of this method with respect to the glycosyl donors (Table 3). A broad array of donors could be installed onto **12** with high 1,2-*cis* selectivities. Glucopyranosyl donors bearing acetyl (**27a**), benzylidene (**27b**), *tert*-butyldimethylsilyl (**27c**), and methyl (**27d**) protecting groups could be used. Moreover, galacto- (**27e**) and fucopyranosyl (**27f**) groups were installed with similar efficiencies and selectivities. Disaccharide donors (**27g**) participate in this reaction uneventfully. Our method could be applied in the stereoselective preparation of various 1,2-*cis*-pentopyranosides, which include xylopyranosides (**27h**), arabinopyranosides (**27i**) and lyxopyranosides (**27j**). It is demanding to build 1,2-*cis*-furanosides, as both electronic

Table 2 | Scope of acceptors

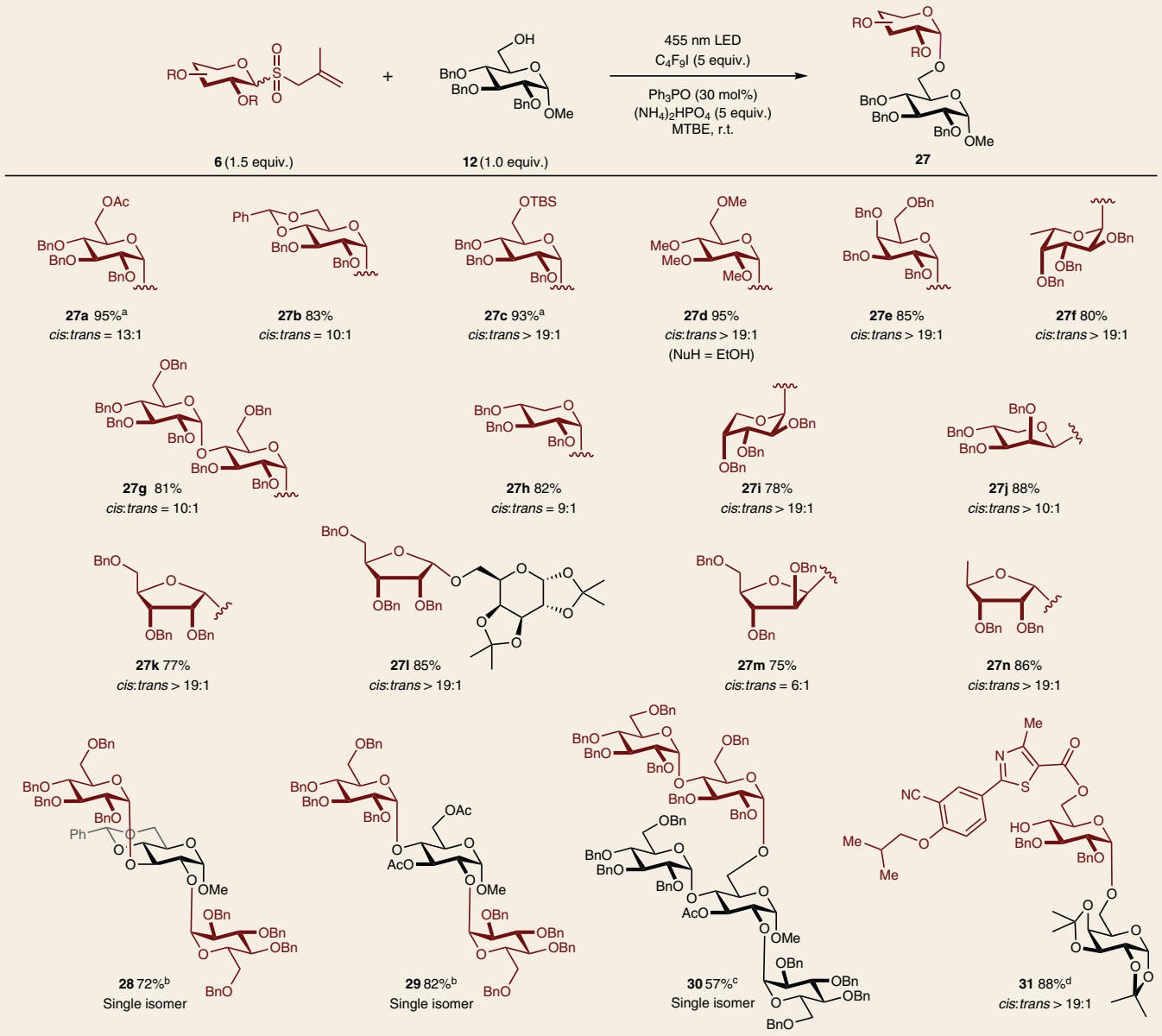




26a	26b	26c	26d	26e	26f	26g	26h	26i
84%, α:β = 10:1	81%, α:β = 12:1	66%, α:β = 8:1	83%, α:β = 10:1	76%, α:β = 8:1	63%, α:β > 19:1	81%, α:β = 11:1	89%, α:β > 19:1	76%, α:β = 11:1
26j	**26k**	**26l**	**26m**	**26n**	**26o**	**26p**	**26q**	
82%, α:β > 19:1	76%, α:β = 11:1	66%, α:β = 7:1	93%, α:β = 16:1	68%, α:β > 19:1	87%, α:β > 19:1	92%, α:β = 15:1	91%, α:β = 10:1	
26r	**26s**	**26t**	**26u**	**26v**	**26w**			
90%, α:β > 19:1	92%, α:β = 16:1	95%, α:β > 19:1	58%, α:β > 19:1	81%, α:β > 19:1	80%, α:β > 19:1			
26x	**26y**	**26z**	**26aa**	**26ab**				
78%, α:β = 15:1	65%, α:β = 15:1	60%, α:β > 19:1	81%, α:β = 7:1	92%, α:β > 19:1				
26ac	**26ad**	**26ae**	**26af**	**26ag**	**26ah**			
83%, α:β > 19:1	57%, α:β = 11:1	81%, α:β > 19:1	86%, α:β = 7:1	70%, α:β > 19:1	83%, α:β = 8:1			
Podophyllotoxin	Zidovudine	Gemfibrozil	Naproxen	Indomethacin				
26ai	**26aj**	**26ak**	**26al**	**26am**				
50%, α:β = 8:1	70%, α:β = 12:1	85%, α:β > 19:1	77%, α:β > 19:1	87%, α:β > 19:1				

Unless otherwise noted, the reactions in this table were performed at a 0.1 or 0.2 mmol scale in MTBE (0.1 M) at room temperature for 24 h. Isolated yields are reported. Diastereomeric ratios were determined by NMR analysis. See Supplementary Section 5 for experimental details. TBS, *tert*-butyldimethylsilyl, Trt, trityl.

Table 3 | Scope of donors



Unless otherwise noted, reactions in this table were performed at a 0.1 or 0.2 mmol scale in MTBE (0.1 M) at room temperature for 24 h. Isolated yields are reported. Diastereomeric ratios were determined by NMR analysis. [a]1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose was used as the acceptor. [b]Donor (0.4 mmol), acceptor (0.1 mmol) and C_4F_9I (1.2 mmol) were used. [c]Donor (0.1 mmol), acceptor (0.05 mmol) and C_4F_9I (0.5 mmol) were used. [d]Donor (0.05 mmol), acceptor (0.1 mmol) and C_4F_9I (0.5 mmol) were used. See Supplementary Section 6 for experimental details.

and steric effects favour the formation of the 1,2-*trans* products[53]. Interestingly, our method could be adopted to construct 1,2-*cis*-furanoside linkages as well. For example, ribosides (**27k** and **27l**), arabinofuranosides (**27m**) and 5-deoxyribosides (**27n**) have been generated with good 1,2-*cis* selectivities. Notably, many of the glycosyl iodides involved in these reactions have not been reported, which could be because they are too reactive to generate and isolate or manipulate by the conventional (ionic) methods. Last, we applied this method in the synthesis of trisaccharides (**28** and **29**) and pentasaccharides (**30**). To further illustrate the functional-group tolerance of our method, we demonstrated that highly elaborated donors (such as **31**) can be used directly in our reaction. From the above examples, we point out that the high 1,2-*cis* selectivity of our glycosylation method does not rely on the relative configuration and reactivity of donors[54].

Further mechanistic studies. General 1,2-*cis*-glycosylation methods are highly important but remain much underdeveloped[24,36,37]. A mechanistic understanding of the general and high 1,2-*cis* selectivity displayed by our reaction might be valuable to address this challenge. Prior studies suggest that the stereoselectivity of reactions involving glycosyl iodide intermediates is governed by the Curtin–Hammett principle[10,43]: the α- and β-configured glycosyl iodides are in rapid equilibrium, and the latter more reactive to afford the 1,2-*cis*-glycosides preferentially. We conducted density functional theory calculations to gain structural insights into the origin of this stereoselectivity (Fig. 3a). In our model system, we employed ethanol as the nucleophile and *cis*- or *trans*-glycosyl iodides (**32** or **33**) as the electrophile. From the computed energy diagram, the interconversion between iodides **32** and **33** via **TS-IV** is, indeed, highly facile, and the reactions between ethanol and **32** or **33** are the

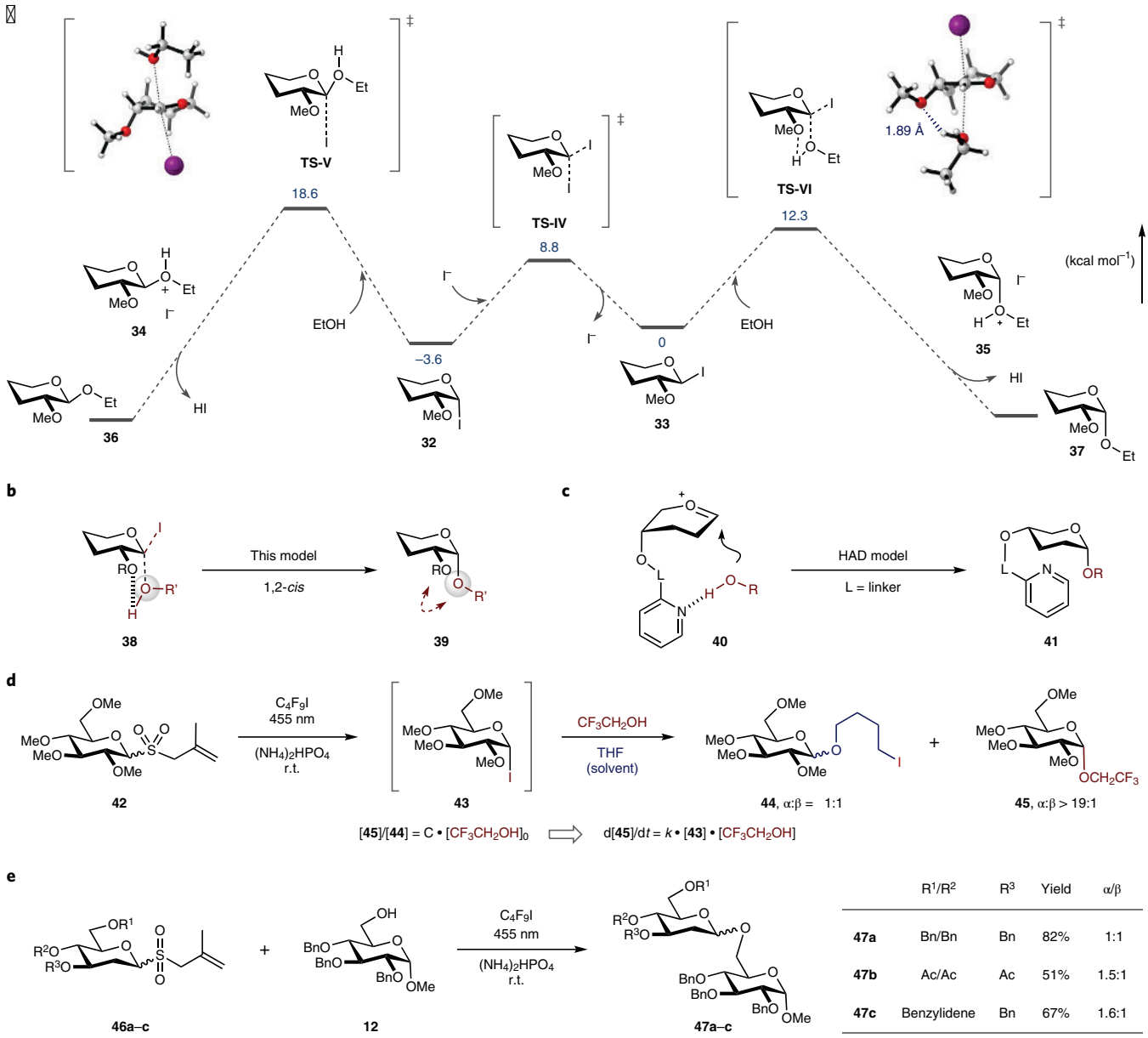


Fig. 3 | Mechanistic explanation for 1,2-*cis* selectivity. a, Computed energetics for the reaction between model substrates **32** and **33** and ethanol. The results show that the reactions between glycosyl iodides and alcohols are governed by the Curtin–Hammett principle. **b**, C2-alkoxy-directed glycosylation model. The nucleophile forms a hydrogen bond with the C2-alkoxy group of the donor, and thus preferentially affords 1,2-*cis*-glycosides. **c**, Demchenko's hydrogen-bond-mediated aglycone delivery (HAD) model. The nucleophile forms a hydrogen bond with the pyridine unit preinstalled onto the donor to afford products with desired configurations. **d**, Competing trap of glycosyl iodide **43** by THF solvent versus trifluoroethanol. The ratio of **45** and **44** formed increases linearly with the amount of CF_3CH_2OH initially added, which suggests the trapping rate of **43** has a first-order dependence on the concentration of CF_3CH_2OH (see Supplementary Section 3.5 for a detailed discussion). In the equation, C stands for a constant, and *k* indicates rate constant. **e**, Glycosylation using 2-deoxy donors **46a–46c**. The use of 2-deoxy donors gave glycoside products in poor α/β ratios, which highlights the importance of the C2-alkoxy group in controlling the stereoselectivities by forming a hydrogen bond with the acceptors. Free energies were computed by ωB97X-D/def2tzvp/SDD/SMD (Et_2O)//ωB97X-D/6-31G(d)/Lanl2dz/SMD (Et_2O).

rate-determining steps. We located transition structures **TS-V** and **TS-VI** that would lead to 1,2-*trans*-glycoside **36** (via **34**) and 1,2-*cis*-glycoside **37** (via **35**), respectively. Consistent with the experimental results, **TS-V** is lower in energy than **TS-VI** by 6.3 kcal mol^{-1} (see Supplementary Fig. 8 for other conformers of **TS-V** and **TS-VI**). Further scrutiny of **TS-VI** revealed an intriguing structural feature: the hydroxyl group of the incoming nucleophile (ethanol) and the C2-methoxy group of the electrophile **33** form a strong hydrogen bond (1.89 Å) (Fig. 3a). In contrast, such an interaction is absent or unattainable in **TS-V**. Similar observations were also made for the analogous five-membered ring systems (Supplementary Fig. 9).

We thus proposed a model depicted in Fig. 3b to explain the general 1,2-*cis* selectivities observed in our study: the formation of hydrogen-bond complex **38** renders the attack of the nucleophile pseudo-intramolecular[55], which preferentially afforded the 1,2-*cis* product **39**. It is instructive to compare our model with the hydrogen-bond-mediated aglycone delivery[56–59] model proposed by Demchenko's group (**40** and **41**, Fig. 3c), in which a judiciously

installed pyridine unit forms a hydrogen bond with the incoming nucleophile and guides its approaching trajectory towards the glycosyl electrophile. Regardless, we emphasize that, although the C2 substituent (for example, acetates) has been widely employed to achieve selective 1,2-*trans*-glycosylation in carbohydrate synthesis, its potential as a handle for 1,2-*cis*-glycosylation remains barely explored[60].

Our proposed stereodirecting model is also supported by two sets of experimental results. In the first, we conducted our glycosylation reaction between **42** and CF_3CH_2OH under the standard conditions, except we used THF as the solvent (Fig. 3d). We noted that a mixture of **44** (which arises from a THF attack) and **45** (which arises from a CF_3CH_2OH attack) formed. Interestingly, the formation of **45** is highly stereoselective, whereas that of **44** is not. Incidentally, THF is a nucleophile devoid of a hydrogen-bond donor, and thus incapable of forming a complex with the C2-methoxy group of **43** (as in **38**). We next performed a series of such glycosylation reactions that differed only by the initial concentrations of CF_3CH_2OH ($[CF_3CH_2OH]_0$) added. When the reactions were stopped at the early stages, we found that the ratio [**45**]/[**44**] increased almost linearly with $[CF_3CH_2OH]_0$. These results indicate that the formation of **45** has a first-order dependence on the concentration of CF_3CH_2OH (see Supplementary Section 3.5 for more detailed discussions), consistent with the models shown in Fig. 3a,b. To further substantiate our hypothesis, we reacted **12** with various 2-deoxy glycosyl donors (with the general structure of **46a**–**46c**) that lack the C2-alkoxy directing group (Fig. 3e). We found products **47a**–**47c** were formed in low diastereomeric ratios in all these cases, which highlights the role of the C2-alkoxy groups in the glycosyl donors for controlling the stereoselectivities in our reaction.

Discussion

In summary, by exploiting a radical-based donor activation strategy, we developed a general, simple and mild method to construct the challenging 1,2-*cis*-glycosidic bonds. This method avoids the use of sensitive substrates, acidic reagents or elaborate (metal) catalysts. Experimental and computational studies suggest that the activation of glycosyl donors in this reaction is achieved by a XB-assisted, light-promoted single-electron transfer cascade, which converts bench-stable allyl glycosyl sulfones into glycosyl iodides via the intermediacy of glycosyl radicals under extremely mild conditions. The unique reaction mechanism endows the reaction with excellent functional-group tolerance. As an additional, important advantage of this method, a broad array of glycosyl units can be installed with high 1,2-*cis* selectivities. Mechanistic studies indicate that the C2-alkoxy group can serve as an effective 1,2-*cis*-directing group to build glycosidic bonds. The generality of this strategy implies that, compared with the conventional ionic activation strategies, radical activation of donors can be a fruitful platform for the development of glycosylation reactions. Some of these possibilities are under investigation in our laboratories.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-022-00918-z.

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Methods

To an 8 ml screw-capped vial that contained a magnetic stir bar was sequentially added an allyl glycosyl sulfone (0.3 mmol, 1.5 equiv.), a nucleophile (0.2 mmol, 1.0 equiv.), Ph_3PO (0.06 mmol, 0.3 equiv.), $(NH_4)_2HPO_4$ (1.0 mmol, 5.0 equiv.), C_4F_9I (1.0 mmol, 5.0 equiv.) and MTBE (1 ml) under N_2 atmosphere. The vial was tightly sealed with a Teflon-lined cap and allowed to stir for 24 h at room temperature, with irradiation from a 40 W, 455 nm LED bulb placed ~3 cm below it. The reaction mixture was then diluted with ethyl acetate (10 ml) and filtered through a pad of cotton. The combined organic phases were concentrated 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 the paper and its Supplementary Information files.

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Author contributions

D.N. conceived the idea, guided the project and wrote the manuscript with feedback from other authors. C.Z. made the initial observations and analysed the results. C.Z., H.Z. and Q.-D.D. explored the substrate scope and performed the mechanistic studies. Y.Z., G.Y.L. and C.Z. performed the density functional theory calculations on the reaction mechanism under the advice of K.N.H.

Competing interests

The authors declare no competing interest.

Additional information

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