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Communication

Selective Isomerization via Transient Thermodynamic Control: Dynamic Epimerization of *trans* to *cis* Diols

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ABSTRACT: Traditional approaches to stereoselective synthesis require high levels of enantio- and diastereocontrol in every step that forms a new stereocenter. Here, we report an alternative approach, in which the stereochemistry of organic substrates is selectively edited without further structural modification, a strategy with the potential to allow new classes of late-stage stereochemical manipulation and provide access to rare or valuable stereochemical configurations. In this work, we describe a selective epimerization of cyclic diols enabled by hydrogen atom transfer photocatalysis and boronic acid mediated transient thermodynamic control, selectively generating less stable *cis* products from the otherwise favored *trans* isomers. A range of substitution patterns and ring sizes are amenable to selective isomerization, including stereochemically complex polyols such as estriol, as well as *syn* to *anti* epimerization of acyclic vicinal diols. Moreover, this strategy has enabled the divergent epimerization of saccharide anomers, providing access to distinct sugar isomers from α- or β-configured glycosides.

Building, preserving, and manipulating the stereochemistry of organic molecules has long been a cornerstone of structural synthetic chemistry.[1] In particular, tetrahedral sp^3 chirality represents the most common element within stereochemistry, and is typically derived from bond-forming steps that require high levels of kinetically selective substrate- or catalyst-induced stereocontrol. Recently, we envisioned an alternative strategy for stereoinduction, termed dynamic stereocontrol,[2] wherein the chirality-defining events are decoupled from the main framework-forming steps, a strategy that could allow for late-stage flexibility in generating enantiomers or diastereomers from a single stereoadaptive molecule. While stereochemical interconversion has been a critical design element in a number of important methodologies, not least of which dynamic kinetic resolutions,[3] these are typically centered around the kinetic removal or conversion of a functional group that can enable proximal stereochemical flux (e.g., α-ketones, amines, olefins, etc.).[1b,4a,2,4b,c] In this study, we explore an underutilized catalysis concept, namely transient thermodynamic control, whereby a simple additive or template can temporarily alter the relative stabilities of a mixture of stereoisomers (e.g., enantiomers, diastereomers, etc.), thereby allowing a thermodynamic shift in ground state populations upon subjection to stereochemical equilibration. As a specific embodiment, we disclose the one-step, catalytic conversion of cyclic *trans* diols to their *cis* diol counterparts with uniform diastereocontrol. This new diol isomerization protocol is accomplished via the combination of hydrogen atom transfer (HAT) and boronic ester metathesis, a protocol we expect will be of utility to a wide range of practitioners of organic molecule construction.

When considering the design of dynamic stereochemical transformations, two primary challenges present themselves: the rapid interconversion between stereoisomers and the selection of a single isomer from a dynamically equilibrating mixture (Figure 1). As the products of epimerization reactions are structurally similar to the substrates, this selectivity frequently derives from differences between epimers in either thermodynamic stability or kinetic susceptibility to further conversion. Consequently, epimerization mechanisms that selectively produce less stable or more reactive isomers via a one-step catalytic process—termed out-of-equilibrium processes—remain generally elusive in the art. Indeed, in a thermodynamically controlled isomerization, selectivity derives from the relative stabilities of the possible isomers, wherein the most stable species must be the major product. By the implementation of transient thermodynamic control, we envisioned the possibility of altering this equilibrium with a template that would selectively stabilize and sequester an otherwise thermodynamically disfavored isomer, making that complex a transient thermodynamic sink. As a necessary consequence, dynamic stereointerconversion would then enforce formation of the desired "uphill" diastereomer rather than the most stable isomer of the free substrate (Figure 1).

We were drawn to diols and boronic acids as an attractive pairing of substrate and template to demonstrate transient thermodynamic control in a practical epimerization reaction. Diols and polyols are ubiquitous motifs in natural products and biologically relevant molecules, and boronic acids are well-known to reversibly associate with diols to form boronic esters under mild conditions.[5] Cyclic diols exhibit clear stereochemical preferences in esterification, with *cis* diols more

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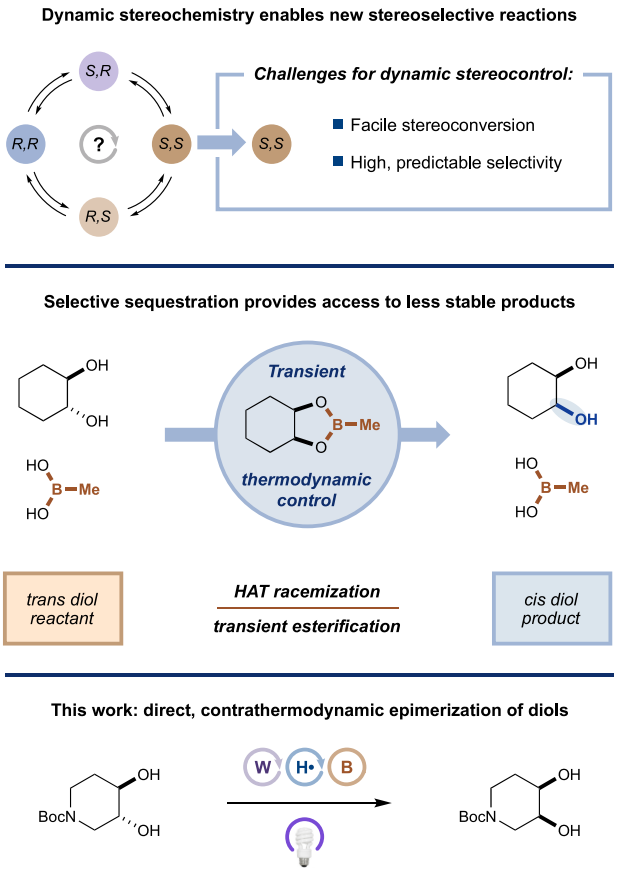

Figure 1. Epimerization via transient thermodynamic control.

readily forming boronic esters than their *trans* counterparts.[6] Thus, the relative stabilities of these diol isomers are transiently inverted in the presence of boronic acids.[7] This ring-strain-based thermodynamic inversion has been exploited for a number of resolutions of diastereomeric cyclic diols,[6] while elegant studies from Taylor on site-selective carbohydrate protection and functionalization have revealed the utility of ring chelation.[8] While boronic esters are stable under anhydrous conditions, hydrolysis or transesterification under mild conditions will readily liberate the free diol (and boronic acid).

Drawing inspiration from our laboratory's previous successes in using hydrogen atom transfer (HAT) across a diverse series of transformations,[9] we chose to pursue an open-shell, HAT strategy for diol epimerization. More specifically, repeated nonselective HAT events would racemize the alcohol stereocenters, resulting in the necessary dynamic equilibration between all stereoisomers. As both facile α-oxy radical generation and subsequent hydrogen abstraction are necessary for dynamic epimerization, we selected the decatungstate anion and thiophenol as a complementary pair of HAT catalysts. Upon near-UV irradiation, excited-state decatungstate is capable of abstracting hydrogen atoms from strong, unactivated C(sp^3)–H bonds with high rates (10^7 M^{-1} s^{-1} for cyclohexane) and predictable site selectivity for the most sterically accessible, electron-rich bond.[10] Polarity matched α-oxy HAT via thiols such as thiophenol is likewise rapid due to the weak, protic nature of the S–H bond (10^8 M^{-1} s^{-1} for an isopropyl radical).[11]

A depiction of our reaction design is shown in Figure 2. Repeated hydrogen atom abstraction/donation by decatungstate anion and thiophenol, respectively, is expected to lead to an equilibrium mixture containing both *trans* (**1**) and *cis* (**3**) diol isomers ($\Delta G_{calc\ cis-trans}$ = 1.1 kcal mol^{-1}; see Supporting Information for details). Methylboronic acid present in the system would favorably undergo esterification with the *cis* diol, forming the stable *cis* boronic ester **5**. Conversely, formation of *trans* boronic ester **4** is relatively disfavored due to ring strain and thus is predicted to be only a minor component. Additionally, boronic ester formation should be reversible, allowing any of the *trans* boronic ester **4** that may form to revert to the *trans* diol.[12] As this dynamic system undergoes equilibration, the most stable species, i.e. *cis* boronic ester **5**, should rapidly predominate. Upon reaching a thermodynamic equilibrium, a simple hydrolytic workup would deliver the less stable *cis* diol diastereomer in a single synthetic step from the more-stable *trans* isomer without any reagent consumption.

Our experimental investigations began by combining *trans*-1,2-cyclohexanediol, methylboronic acid, and catalytic amounts of tetrabutylammonium decatungstate and thiophenol in anhydrous acetonitrile under near-UV irradiation (Kessil 34 W 390 nm LEDs) at room temperature. Pleasingly, *cis* diol boronic ester was generated (14% yield), with *trans* diol largely remaining. Further evaluations revealed that replacement of thiophenol with diphenyl disulfide substantially increased the efficiency (65–70% yield). As S–S bonds are known to homolyze upon irradiation with blue or near-UV light,[13] we hypothesized that the use of a disulfide generates both the active thiophenol HAT catalyst and improves the rate of decatungstate turnover.[14] Combining a better-soluble tetrabutylphosphonium counterion with irradiation from a more powerful 365 nm light source (the Integrated Photo-

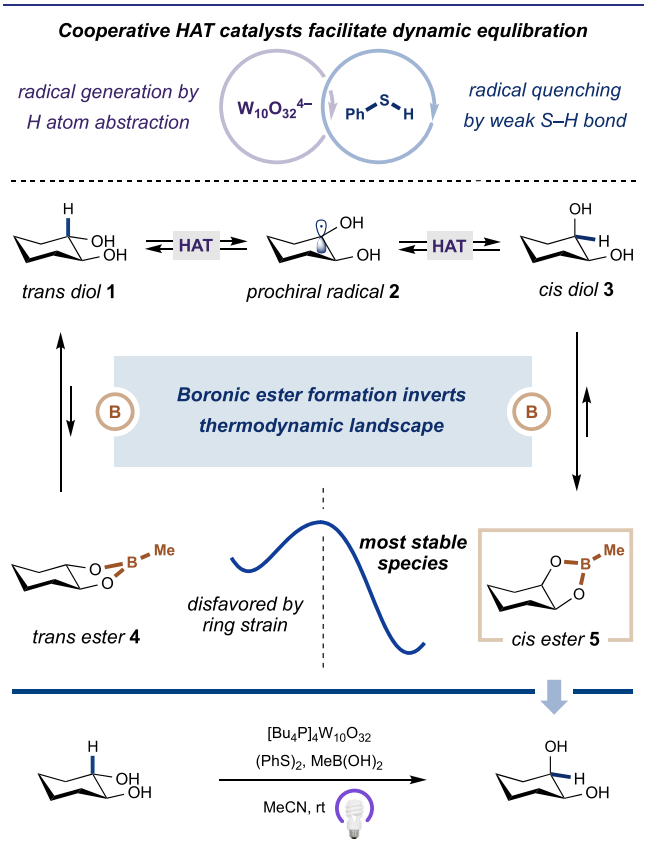

Figure 2. Reaction design of the selective epimerization.

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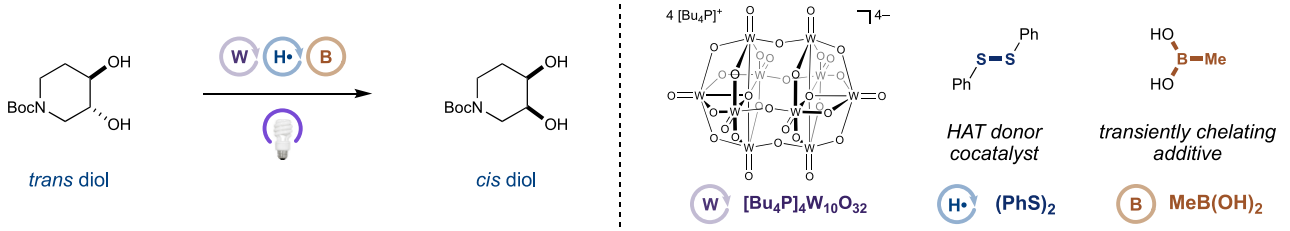
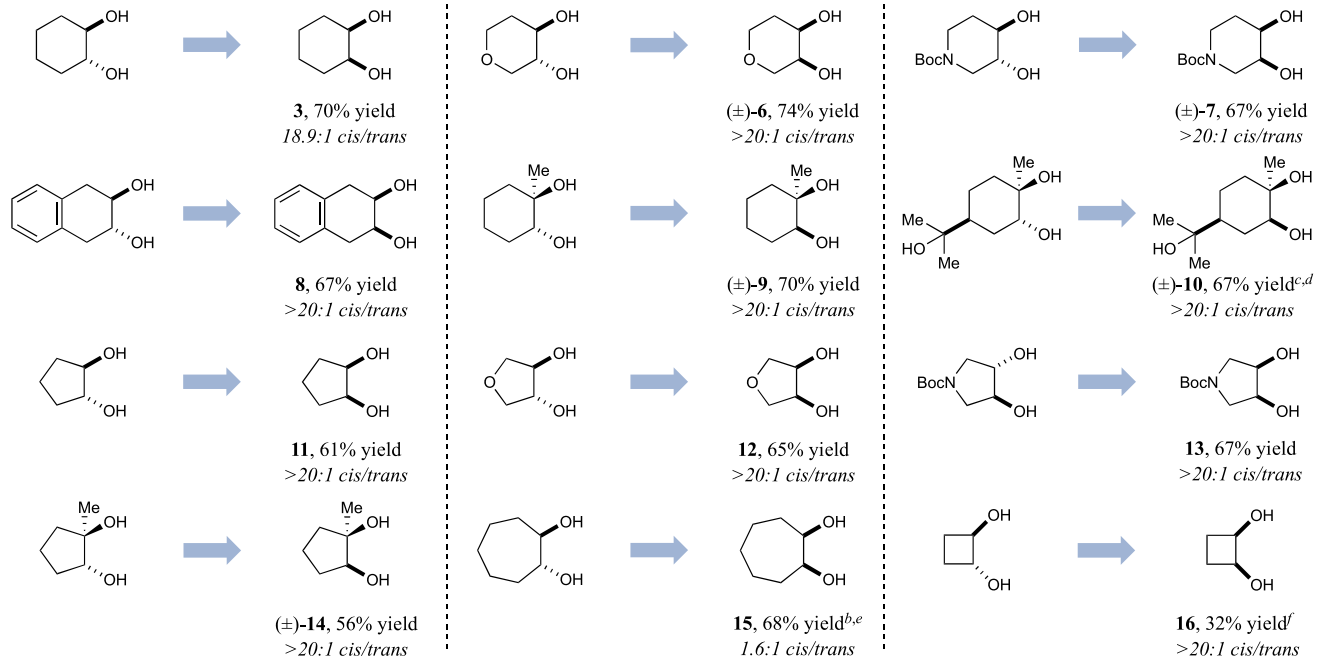
Table 1. Scope Evaluation of *trans*-1,2-Diols[a]





[a]Standard conditions: 0.5 mmol of *trans* diol, 1.25 equiv of $MeB(OH)_2$, 0.5 mol % $(PBu_4)_4W_{10}O_{32}$, 50 mol % $(PhS)_2$, MeCN (0.1 M), 12−36 h of irradiation with a 365 nm LED plate in the Integrated Photoreactor at 20−30 °C then 1.5 equiv of pinanediol, 5 equiv of K_2CO_3, 4−24 h. See Supporting Information for full experimental details. All yields are isolated as single diastereomers unless noted otherwise. [b]Isolated as a mixture of diastereomers. [c]4 h of irradiation. [d]Analytical yield from ^1H NMR vs mesitylene. [e]35 equiv of H_2O added. [f]1 mol % $(PBu)_4W_{10}O_{32}$. [g]Acyclic diol conditions: 0.1 mmol scale, 1% $(PBu_4)_4W_{10}O_{32}$, 24 h irradiation, isolated as a mixture of diastereomers from five combined reactions. [h]2 mol % $(PBu_4)_4W_{10}O_{32}$, 4:1 MeCN/*t*-BuOH (0.02 M) as solvent.

reactor)[15] further improved the yield to 74% while reducing the requisite reaction time (3 h).[16] Critically, omission of any reaction component resulted in a minimal yield of *cis* product. Moreover, the same epimerization protocol beginning with either *cis*- or *trans*-1,2-cyclohexanediol in the absence of boronic acid provided a 1:1.8 *cis*/*trans* proportion of diol isomers, compared to the 17.5:1 *cis*/*trans* ratio obtained when the acid was incorporated (see Supplementary Table S3).

With these optimized conditions in hand, we moved on to investigate the scope of this new transient dynamic reaction. A

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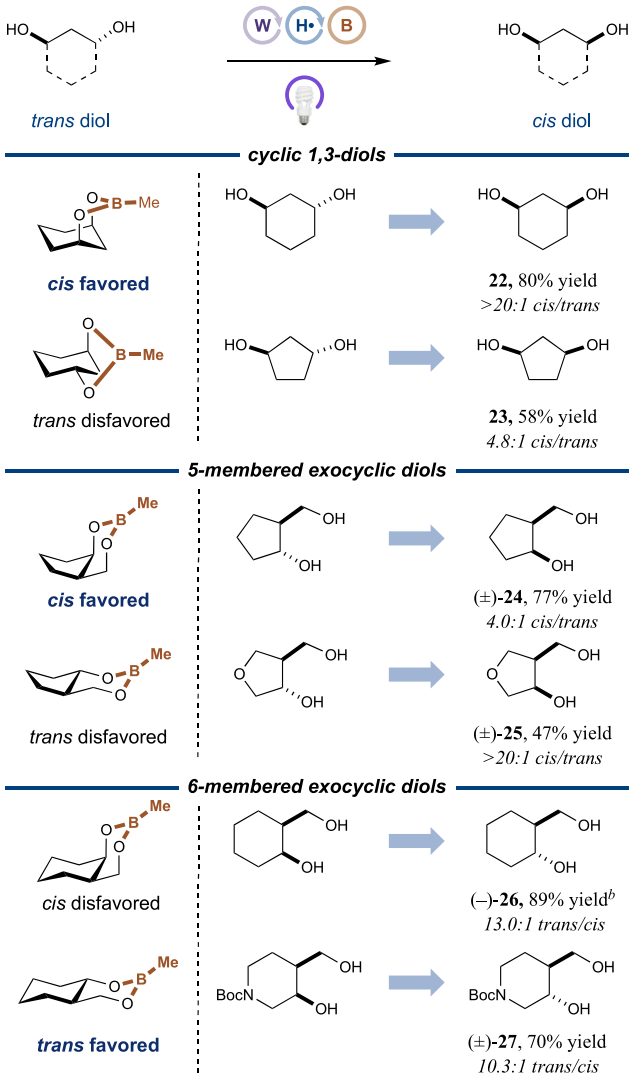
variety of cyclic 1,2-*trans* diols were effective substrates, providing the *cis* diol in good yield and high selectivity (Table 1). Six-membered rings were generally effective across a range of substrates, with 1,2-cyclohexanediol giving 66% of the *cis* diol adduct (**3**). Heterocyclic substructures were also tolerated, with tetrahydropyran and piperidine cores efficiently converted to the less stable isomers in 74% and 67% yield, respectively (**6**, **7**). While weak benzylic C−H bonds provided four additional competitive sites of abstraction, we were pleased to find that 2,3-*trans*-tetralindiol was readily converted (**8**, 67% yield). We were also pleased to find that five-membered cyclic diols were also effective, with *trans*-1,2-cyclopentanediol and heteroatom-containing analogs (**11**−**13**) generating the *cis* products after dynamic control. Additionally, secondary-tertiary diols were converted to the *cis* diol products in good to excellent yield (**9**, **10**, **14**, 56−70% yields) despite the additional steric hindrance imposed by fully substituted carbon centers and access to a single α-oxy methine site. Menthanetriol **10** additionally highlights that the standard epimerization conditions can tolerate additional alcohols or stereocenters. To demonstrate the generality of this chelation-based selectivity principle for a variety of ring sizes, we successfully converted the conformationally flexible *trans*-1,2-cycloheptanediol to the *cis* diastereomer (**15**), despite the small stability difference between *cis*- and *trans*-fused 5/7 ring systems.[17] Additionally, 4-membered substrates were competent: *cis*-1,2-cyclobutanediol (**16**) could be produced from the more stable *trans* isomer in a modest 32% yield.

Acyclic diols were also investigated as potential substrates for epimerization. For acyclic vicinal diols, the most stable transient boronic ester has substituents in an *anti* configuration and, accordingly, *anti* diols were obtained with good yields and selectivities in several cases (**17**−**19**, 77−92% yields). In particular, substrates **18** and **19** highlight the synthetic utility of this method by converting 1:1 mixtures of diastereomers to a highly stereoenriched product. Pleasingly, more stereochemically complex and biorelevant polyols were also amenable to epimerization: the human estrogen estriol was isomerized to its 16-β epimer (**20**) in a low but synthetically useful 37% yield, providing a hormone analog in a single operation. A diol-containing derivative of the pharmaceutical compound oxaprozin was also competent, achieving dynamic control in the presence of an electron-rich diaryloxazole and weak α-aryl, α-amino, and α-carbonyl C−H bonds (**21**, 51% yield).

We next became interested in extending this methodology to 1,3-diol substrates (Table 2). We expected that, consistent with our mechanistic design, the diol isomer capable of forming the most stable bicyclic boronic ester should be the major product of epimerization. Indeed, this hypothesis proved correct, with *trans*-1,3-cyclohexanediol and its cyclopentane analog converted to *cis* isomers **22** and **23** (80% and 58% yield, respectively) due to the highly disfavored nature of potential *trans*-bridged bicyclic esters.[6a] Five-membered exocyclic diols were also transformed to *cis* epimers **24** and **25** (77% and 47% yield, respectively) due to the less strained *cis* ring fusion of a 6/5 bicyclic boronic ester. Conversely, 6/6 bicyclic ester intermediates favored a *trans* arrangement of stereocenters (**26**, **27**), analogous to the higher stability of *trans*-decalin relative to its *cis* isomer.

Finally, we sought to apply our transient dynamic concept to saccharides and their derivatives, a particularly important class of polyols given their prevalence in nature and high density of stereochemical information.[18] The interconversion of saccharide stereochemistry to afford rare sugars from abundant precursors (e.g., glucose) has been a long-standing challenge and is the subject of recent studies by the Wendlandt group, utilizing a combined photoredox/HAT system to selectively epimerize saccharides.[4b] As the selective interactions of boronic acids with sugars have been studied extensively for both synthetic and sensing purposes,[5,19] we anticipated that formation of the transient chelate should be both facile and selective, and could potentially provide unique epimerization selectivity. Indeed, we were delighted to find that increasing the equivalents of methylboronic acid allowed for chelation at both C4/C6 and C2/C3, enabling the selective C2 epimerization of D-α-methylglucose to D-α-methylmannose (**28**) in 47% yield (Table 3). Perhaps most surprising, inverting the configuration of the anomeric carbon led to a dramatic change in site-selectivity: D-β-methylglucose was thus transformed to the rare sugar D-β-methylallose (the C3 epimer) in 62% yield (**29**). This switchable selectivity is noteworthy in the context of stereochemical manipulations of sugars; while selective glycosylation chemistry is well-investigated for setting the anomeric C1 stereocenter in a

Table 2. Scope Evaluation of 1,3-Diols[a]



[a]See Supporting Information for experimental details. All yields are isolated. [b]Isolated as a mixture of diastereomers.

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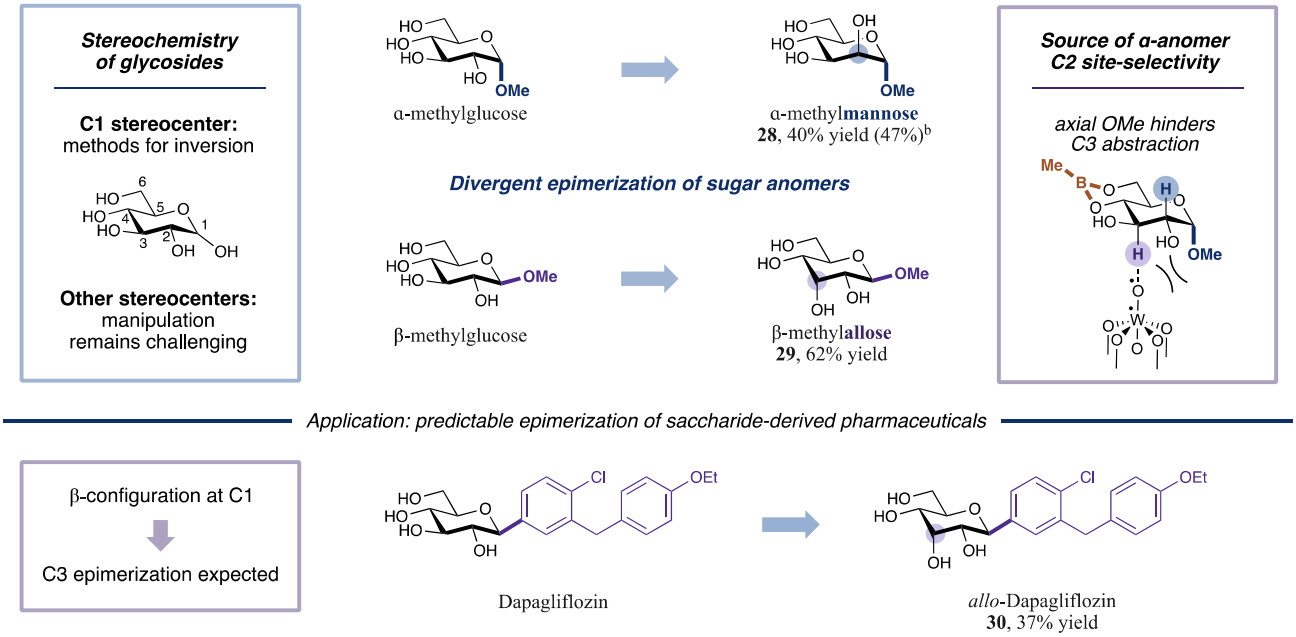
Table 3. Divergent Epimerization of Glycosides[a]



[a]See Supporting Information for experimental details. All yields are isolated unless noted otherwise. [b]Assay yield from ^{1}H NMR vs mesitylene.

variety of saccharides,[20] there are relatively few methods for manipulating the stereochemistry at other positions.[21,4b] Indeed, the transformation of a single sugar isomer into divergent sugars based solely on the anomeric configuration is, to our knowledge, previously unknown.

Intrigued by this divergent selectivity, we considered its possible origins. Selective reactivity at the C3 position of sugars has previously been observed, consistent with our results for *β*-configured glycosides.[21,4b,22] However, this selectivity is typically independent of anomeric configuration, and its basis is not completely understood. The C2 epimerization observed for D-*α*-methylglucose under our conditions is, however, comparatively uncommon. We propose that the origin of this selectivity is kinetic in nature: decatungstate is known to preferentially abstract from less sterically hindered C−H sites, and abstraction is especially disfavored from C−H bonds with coaxial substituents.[10] For *α*-methylglucose, the axial methoxy group hinders abstraction from the otherwise favored C3 C−H bond, leading to the observed C2 selectivity. To test this hypothesis, we subjected a structurally related compound to undergo dynamic inversion. The C-glycoside pharmaceutical dapagliflozin contains a *β*-configured diarylmethane group, and therefore C3 epimerization to the *allo* isomer was expected. After epimerization, *allo*-dapagliflozin (**30**) was in fact obtained, albeit in a modest 37% yield. As such, this platform provides a predictive method for site-selective epimerization of saccharides and their derivatives based on the stereochemical orientation of the anomeric position.

In conclusion, we have demonstrated that transient thermodynamic control is an effective design principle for the generation of energetically uphill products. Employing methylboronic acid as a key chelating additive, a range of cyclic diols and polyols underwent stereoconvergence to their *cis* isomers under an HAT manifold. We anticipate that this protocol, and transient thermodynamic control as a concept more broadly, will expand the potential scope of known transformations and enable additional strategies for late-stage functionalization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c11552.

Experimental details, materials, methods, computational studies, and spectral and characterization data (PDF)

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Notes

The authors declare the following competing financial interest(s): A competing financial interest with respect to the Integrated Photoreactor.

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