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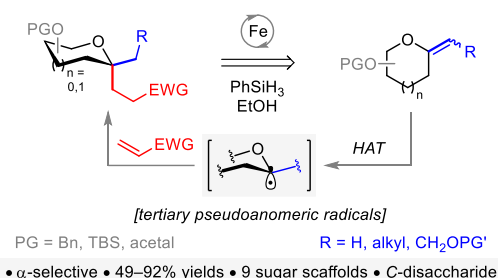
Stereoselective Synthesis of C,C-Glycosides from Exo-Glycals Enabled by Iron-Mediated Hydrogen Atom Transfer

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Supporting Information Placeholder

ABSTRACT: We describe herein a convenient strategy for the construction of C,C-glycoside building blocks via the intermediacy of tertiary pseudoanomeric radicals. Application of an iron-mediated hydrogen atom transfer/Michael-Giese coupling enables the anomeric quaternization of readily available exo-glycals with good to complete stereocontrol in the pyranose and furanose series. Carefully optimized conditions allow the use of challenging trisubstituted derivatives prone to undergo further elaboration to stable neoglycoconjugates. Preliminary results for direct C-disaccharide synthesis are also discussed.



C-glycosides constitute a major class of glycomimetics in which the customary C-O acetal linkage in natural O-glycosides has been substituted for a C-C bond. Such modification confers C-glycosides enhanced stability towards chemical and enzymatic hydrolysis,¹ providing useful probes for studies involving carbohydrate-processing enzymes.² Within this family, C,C-glycosides - also referred to as C-ketosides³ - are characterized by the presence of a stereodefined quaternary pseudoanomeric center bearing two exocyclic C-substituents. Aside from their structural relationship with ulosonic acid derivatives (e.g. N-acetylneuraminic acid), these scaffolds are attractive platforms for the diversification of (one or two) aglycon moieties in stable carbon-linked neoglycoconjugates, as demonstrated by Schmidt *et al.* in the context of galactosyltransferase inhibition (Figure 1).^{4,5} C,C-glycosides also stand as key intermediates *en route* to anomeric spiro-carbohydrates. Those notably include synthetic spiro-nucleoside analogs displaying antiviral, antimetabolic and antibacterial activities,⁶ spiro-lactones,^{7,8} lactams and benzodiazepines as GABA receptor ligands,⁹ as well as syringolide, secosyrin and sphydrofuran natural products.¹⁰ Beyond the latter, ertugliflozin¹¹ (SteglatroTM), a selective SGLT2 inhibitor, was recently approved by the FDA for the treatment of type II diabetes. The prevalence of 2,2-disubstituted tetrahydrofurans and tetrahydropyrans in complex molecules including thysiferols,¹² maitotoxin¹³ and pectenotoxins¹⁴ further establishes C,C-glycoside motifs as valuable synthons.

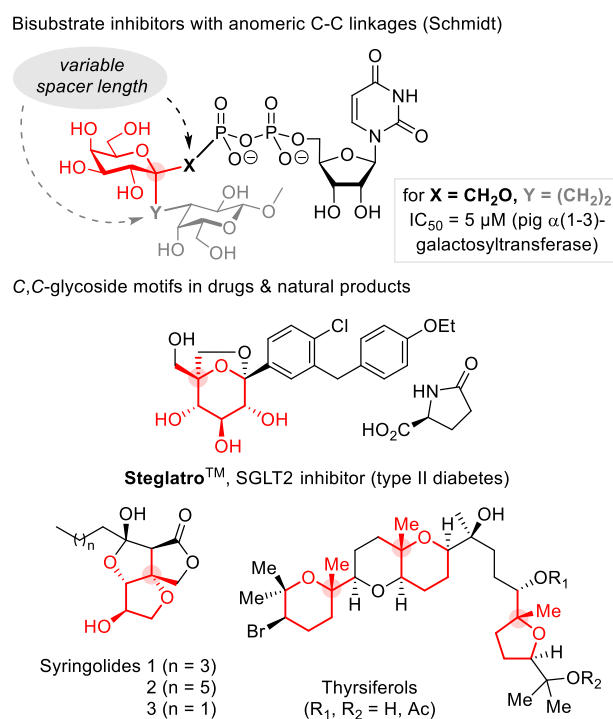


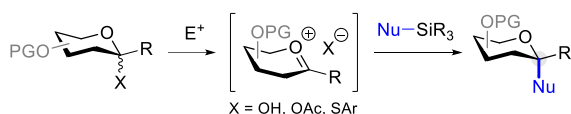
Figure 1. Prevalence of C,C-glycoside scaffolds in bioactive synthetic and natural products.

In sharp contrast with the broad palette of methods targeting C-glycosides,¹⁵ few approaches allow the stereoselective construction of the quaternary pseudoanomeric carbon embedded in C,C-glycosides.¹⁶ This has been mostly accomplished by means of electrophilic activation^{17,18,19} or reductive samarium²⁰ of appropriate sugar donors (Scheme 1). Albeit such reactions can proceed in good

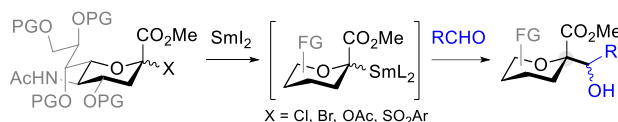
yields with moderate to high stereoselectivities, they display substantial limitations in terms of coupling partners (respectively allylsilanes or aldehydes).²¹

Scheme 1. Established methods for C,C-glycoside synthesis and proposed strategy using HAT catalysis.

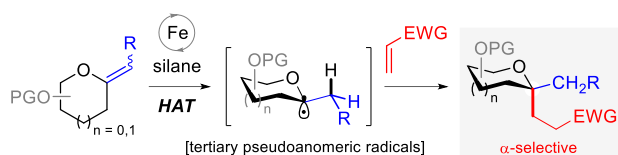
Electrophilic activation of tertiary lactol derivatives



Sm-mediated umpolung of neuraminic acid derivatives



This work: HAT-enabled C,C-glycoside synthesis from *exo*-glycals

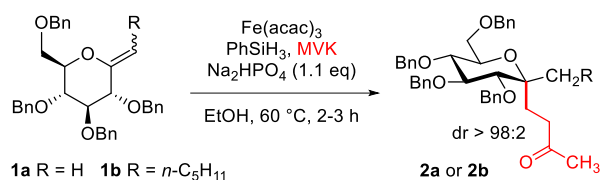


Aiming to establish a convenient route to novel original C,C-glycoside derivatives, we foresaw that a radical-based manifold may provide a useful tool for stereochemical control. Indeed, in the common *D-gluco*, *D-galacto* and *D-manno* series, reactions of pseudoanomeric radicals often display high α -selectivity due to their innate preference for an axial conformation.^{22,23} Furthermore, very small energetic changes in the conformation of glycopyranosyl radicals have been predicted when replacing an anomeric hydrogen with a methyl substituent,²⁴ hinting a predictable stereochemical outcome for the addition of sought-after tertiary pseudoanomeric radicals. However, these reactive intermediates are hardly accessible given the low availability/stability of C-substituted anomeric bromides, sulfides or selenides precursors,²⁵ notwithstanding Suárez's alternative approach involving intramolecular 1,n-hydrogen abstraction which employs specific substrates.^{26,27} When considering alternative manifolds, catalytically generated transition metal hydrides have emerged as outstanding tools for the hydrofunctionalization of electron-rich alkenes with Markovnikov-like selectivity.²⁸ Baran *et al.* have developed an iron-mediated Michael-Giese hydroalkylation of olefins that covers a broad substrate scope and whose mechanism was recently deciphered.^{29,30} Under such conditions, *exo*-glycals could thus be viewed as precursors to C,C-glycosides. Although these C-glycosylidene derivatives have been historically designated as "poor acceptors, even when reacted with electrophilic radicals",^{31,32} two examples of radical azidoselenation³³ and trifluoromethylation³⁴ were recently described. Here, we report the extension of the radical chemistry of *exo*-glycals to C,C-glycoside synthesis by means of iron-catalyzed hydrogen atom transfer (HAT).

To begin our studies, *exo*-glycal **1a** was conveniently prepared from the parent δ -gluconolactone following Guey-

rard's protocol relying on a modified Julia-Kocienski olefination.³⁵ Initial forays using methyl vinyl ketone (MVK) and PhSiH₃ (4 equiv. each) in EtOH (0.1 M) with Fe(acac)₃ as catalyst and Na₂HPO₄ as buffer under air at 60 °C³⁶ led to the conversion of **1a** into the desired C,C-glycoside **2a** resulting from axial radical addition (see the *Electronic Supporting Information* for nOeSY data), albeit competitive, nonselective decomposition complicated its isolation (Table 1). These reactions revealed an interesting trend depending on catalyst loading, which was set to 10 mol% since extensive byproduct formation occurred above this mark (entries 1–3).³⁷ Lowering the excess of PhSiH₃ was detrimental to the reaction efficiency (entry 4).

Table 1. Optimization of the reaction for di- and tri-substituted *exo*-glycals.



entry	compd	[Fe] (mol%)	PhSiH ₃ (equiv)	MVK (equiv)	C (M)	atm	yield (%) ^a
1	1a	5	4	4	0.1	air	46
2	"	10	4	4	0.1	air	61
3	"	20	4	4	0.1	air	21
4	"	10	2.5	4	0.1	air	44
5	"	10	4	4	0.03	air	75
6	"	10	4	4	0.03	Ar	86
7	"	10	4	2	0.03	Ar	85 (A)
8	"	10	4	2	0.03 ^b	Ar	50
9	"	10	4 ^c	2	0.03	Ar	47
10	1b	10	4	4	0.03	Ar	31 ^d
11	"	10	4+4 ^e	4	0.03	Ar	44 ^d
12	"	100	4+4 ^e	4	0.03	Ar	54 ^d
13	"	100	4+4^e	4	0.05	Ar	75^d (B)
14	"	100	4+4 ^e	4	0.1	Ar	47 ^d
15	"	50	4+4 ^e	4	0.05	Ar	46 ^d
16	"	100	4+4 ^e	4	0.05 ^b	Ar	NR ^d
17	"	100	4 ^c	4	0.05	Ar	29 ^d

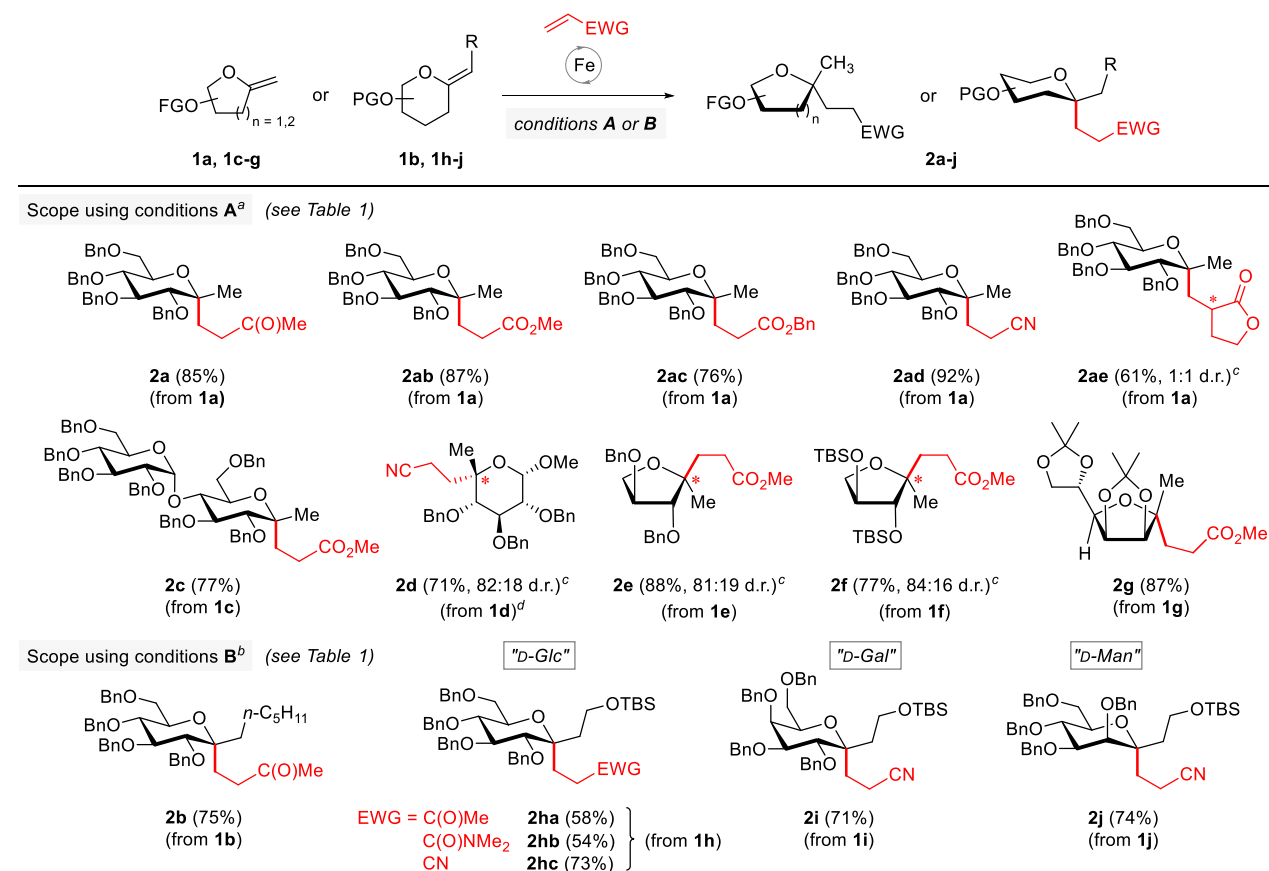
^aIsolated yields. ^bReaction run in 9:1 (CH₂Cl)₂/EtOH. ^c(*i*PrO)PhSiH₂ used in (CH₂Cl)₂ instead of PhSiH₃ in EtOH. ^dReaction quenched after 24 h. ^eSecond portion of PhSiH₃ added after 16 h. NR = no reaction (<5% conversion).

The most significant improvement was observed through the survey of higher dilution conditions: cleaner reaction mixtures were obtained at the cost of longer reaction times, with C = 0.03 M (EtOH) as an optimum (75% of **2a** isolated after 3 h, entry 5); to the best of our knowledge, such trend is infrequent in the area of HAT-initiated C-C bond formation.³⁸ In addition, running the reaction in de-

gassed EtOH under argon further improved its overall efficiency, in line with several related iron-catalyzed protocols (entry 6).³⁹ Under these conditions, the excess of MVK could be reduced to 2 equiv. (entry 7). Attempts to limit the solvolysis rate of PhSiH₃ using dichloroethane/ethanol mixtures⁴⁰ led to reduced yields, as did the use of (iPrO)PhSiH₂ in dichloroethane⁴¹ (entries 8–9). The reactivity of alkyl-substituted *exo*-glycal **1b**⁴² was next assessed using the previously optimized conditions, which engendered the formation of **2b** in 31% yield after 24 h, but without any notable side reaction (65% of **1a** recovered for entry 10). Such reactivity discrepancy between **1a** and **1b** was somewhat unexpected on the basis of recently reported mechanistic studies.³⁹ Indeed, related Fe-catalyzed hydrofunctionalizations have been shown to proceed *via* irreversible HAT to the olefin *via* a low barrier (due to the extremely weak BDE of Fe(III)-H bonds), establishing HAT to the olefin as a fast step in the catalytic cycle.³⁹ Oppositely, the generation of the active iron hydride active species is generally assumed to be turnover-limiting,^{29,30} but clearly proceeded at a sufficient rate to promote the conversion of **1a** (in view of entry 7). Comparatively, since **1b** arguably stands among the most hindered alkenes studied

to date, steric factors may dramatically impact the kinetics of the all-important HAT step.⁴³ An extensive survey of all reaction parameters was therefore undertaken. The isolated yield in **2b** reached 44% when a second portion of phenylsilane was added after 16 h (entry 11), likely countervailing its nonproductive solvolysis to PhSi(OEt)₃ over time.⁴⁴ Increasing the loading in Fe(acac)₃ to 100 mol% also increased the reaction efficiency (entry 12), after which adjusting the concentration to 0.05 M led to an optimum (75% of **2b** isolated, entry 13). Further attempts involving higher concentrations (relative to substrate) or substoichiometric loadings in Fe typically resulted in lower isolated yields (entries 14–15). Notably, reactions run with **1b** in 1,2-DCE/EtOH afforded no product at all (compare entry 16 with entry 8), whereas employing (iPrO)PhSiH₂ in DCE induced clean but low conversion onto **2b** (compare entry 17 with entry 9). Overall, the observed trends suggest that, under moderate dilution conditions (C = 0.05 M) the radical derived from **1b** is less prone to undergo nonproductive pathways, but is harder to generate *via* HAT due to the heavy steric demand around the olefin, thus requiring such forcing conditions.

Scheme 2. Scope of HAT-enabled C,C-glycoside synthesis.



^aReaction time: 1–3 h. ^bReaction time: 20–24 h. ^cDiastereoisomers were not separated (d.r. determined by ¹H NMR analysis). ^dReaction run at 25 °C. Asterisks denote stereocenters at which partial control was observed (major isomer drawn).

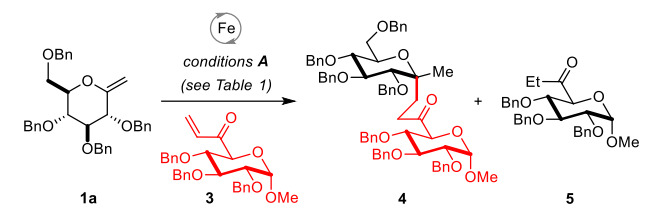
Having established two sets of conditions for converting terminal and substituted *exo*-glycals to *C,C*-glycosides (denoted "A" and "B"), the scope of the reaction was examined (Scheme 2). First, using conditions "A" the HAT-initiated coupling of **1a** with methyl or benzyl acrylate and acrylonitrile afforded the corresponding adducts **2ab-ad** in good to excellent yields. α -Methylene- γ -butyrolactone also behaved as a competent acceptor whose coupling led to **2ae**, albeit no stereoselectivity was observed in the reduction of the resultant electrophilic radical. Of note, attempted reactions with five- and six-membered cyclic enones, vinylsulfones or vinylphosphonates did not afford any coupling products. Pleasingly, maltose-derived *exo*-glycal **1c** reacted smoothly with methyl acrylate to furnish **2c** without cleavage of the *O*-glycosidic bond. Bifunctional glucoside **1d** bearing an anomeric methoxy substituent at C-1 and an *exo*-glycal moiety at C-5 was found to decompose rapidly at 60 °C (and slowly upon storage at -20 °C), but running the reaction at 25 °C in the presence of acrylonitrile gave the expected product **2d** in 71% yield with 82:18 d.r. (*anti/syn*). In contrast with the complete stereoselectivity observed so far in the D-hexopyranosyl series, such erosion may be attributed to an expected chairlike conformation induced by the α -anomeric methoxy group. Indeed, such preference may hamper the adoption of the slightly distorted B_{2,5} boat conformation typical of glucosyl radicals (due to *quasi-anomeric* stabilization by the exocyclic C-O bond)⁴⁵ which overcompensates steric strain and enhances the stereoselectivity of radical coupling, according to Giese.^{22a} This set of conditions was also effective for the coupling of five-membered *exo*-glycals **1e-f** bearing 2,3-*trans*-dibenzyloxy and -disiloxy patterns, providing methyl acrylate adducts **2e-f**. The predominant *anti* radical addition (ca. 4:1 d.r. in both cases) is directed by the neighbouring substituent.^{22a} Finally, *bis*-acetonide **1g** bearing an all-*cis* pattern could be added to methyl acrylate to furnish **2g** with complete stereocontrol.

Aiming to prepare *C,C*-glycosidic scaffolds bearing practical handles for further functionalization, the reactivity of trisubstituted *exo*-glycals was assessed under conditions "B". Attempts to add the D-glucose-derived substrate **1h** to α,β -unsaturated esters were hampered by product transesterification with ethanol, but synthetically useful yields of coupling products **2ha** and **2hb** (54–58%) could be obtained using methyl vinyl ketone and acrylamide as acceptors. Again, the choice of acrylonitrile allowed to improve the efficiency of this challenging reaction, yielding 73% of **2hc** on the mmol scale. The reliability of the protocol was eventually confirmed using derivatives **1i** and **1j**, whose couplings with acrylonitrile granted access to D-galacto (**2i**) and D-manno (**2j**) analogs in similar yields with complete diastereoselectivity.

Finally, we opted to design a sugar-derived acceptor whose radical coupling with an *exo*-glycal could directly generate a carbon-linked disaccharide. In this view, enone **3** was easily prepared from perbenzylated glucuronic acid and treated under conditions "A" in the presence of **1a** (1 equiv each), which led to the expected diglycoside **4** in 33%

yield (Table 2, entry 1). Importantly, formal conjugate reduction of the acceptor was observed, generating **5**: although this process was unexpected under iron(III)-initiated HAT catalysis, Larionov *et al.* have recently shown that electron-poor olefins can add to nickel(II)-ligated Schiff base acceptors.⁴⁶ Yields close to 50% could be reached using 2 equiv of **3** or through a double addition protocol (entries 2–3); conversely, slow addition of **3** by syringe pump over 3 h was unproductive (entry 4), suggesting the need for a sufficient concentration of acceptor to drive the radical coupling. Nevertheless, the reaction proceeded stereospecifically and its yield stands favorably when compared to the xanthate-based *C*-disaccharide synthesis⁴⁷ recently reported by Usui and Hirai, besides allowing the incorporation of an additional substituent in the anomeric position of the donor sugar.

Table 2. Synthesis of carbon-linked diglycoside 4.



entry	deviation from conditions A	yield of 4 (%) ^a	yield of 5 (%) ^b
1	1 equiv 3	33	45
2	none (2 equiv 3)	53	35
3	0.5 + 0.5 equiv 3 ^c	49	43
4	1 equiv 3 added via syringe pump (3 h)	10	17

Full conversion of **1a** was observed after 3 h in all cases. ^aIsolated yield based on **1a**. ^bIsolated yield based on **3**. ^cSecond portion of **3** added after 1.5 h.

In conclusion, a novel manifold for the highly stereoselective construction of *C,C*-glycosides has been devised. Under carefully controlled reaction conditions, the challenging anomeric *C*-quaternization of *exo*-glycals was achieved through a Baran-type iron-mediated HAT/Michael-Giese coupling sequence. Further investigations on the generation of sterically demanding pseudo-anomeric radicals and their applications to the synthesis of novel stable glycoconjugates are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization data, and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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