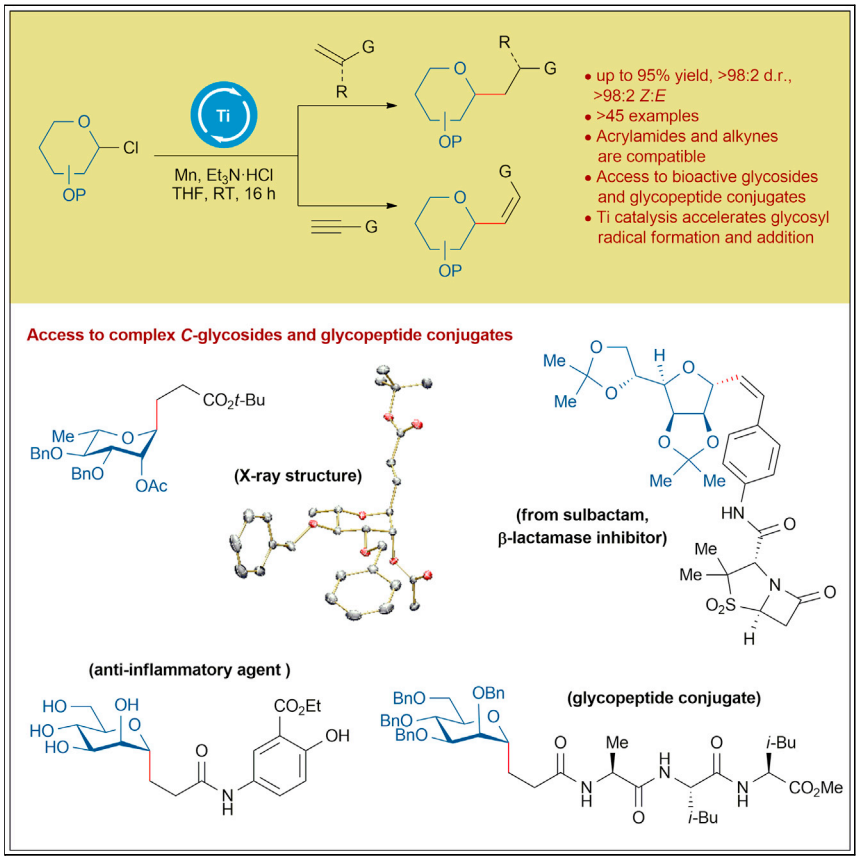
Chem

CellPress

Article

Synthesis of *C*-glycosides by Ti-catalyzed stereoselective glycosyl radical functionalization



The union of glycosyl chloride donors with electrophilic alkenes or alkynes under reductive Ti catalysis provides access to *C*-glycosides in exceptional stereochemical purity. Multifunctional glycoside and glycopeptide conjugate building blocks can be efficiently prepared. Mechanistic studies shed light on the critical role of the Ti-based catalytic species in accelerating glycosyl radical generation as well as glycosyl radical addition across the C–C π-bond, thus facilitating efficient alkylations of less activated acrylamides and alkynes.

Yi Jiang, Quanquan Wang, Xinglong Zhang, Ming Joo Koh

chmqw@nus.edu.sg (Q.W.)
zhang_xinglong@ihpc.a-star.edu.sg (X.Z.)
chmkmj@nus.edu.sg (M.J.K.)

Highlights

A Ti-catalyzed manifold for glycosyl radical alkylation and alkenylation is shown

Readily available glycosyl chlorides are used as glycosyl donors

Activated alkenes, including acrylamides and alkynes, serve as radical acceptors

The method is amenable to the synthesis of bioactive *C*-glycosides and glycopeptides

Jiang et al., Chem 7, 3377–3392
December 9, 2021
https://doi.org/10.1016/j.chempr.2021.09.008

Chem

CellPress

Article

Synthesis of *C*-glycosides by Ti-catalyzed stereoselective glycosyl radical functionalization

Yi Jiang,[1] Quanquan Wang,[1,*] Xinglong Zhang,[2,*] and Ming Joo Koh[1,3,*]

SUMMARY

C-Alkyl glycosides occur widely in nature and are indispensable in drug development programs, owing to their diverse range of medicinal properties. Previous synthetic efforts often utilize stoichiometric reagents, and catalytic methods that afford such glycosides exhibit limited scope. Here, we describe a stereoselective Ti-catalyzed regime that efficiently merges a vast array of readily available glycosyl chlorides with activated olefins, through stereocontrolled glycosyl radical addition to deliver an assortment of *C*-alkyl glycosides. By employing alkynes as radical acceptors, the present strategy is amenable to the synthesis of *C*-alkenyl glycosides bearing a *Z* olefin appendage. The unexpected greater reactivity of glycosyl chlorides (compared with simple tertiary chloroalkanes) in the presence of an organotitanium complex is elucidated through mechanistic and computational studies. Utility of the protocol is underscored by the concise preparation of therapeutically important carbohydrates and glycopeptide conjugates, which are difficult to access using alternative approaches.

INTRODUCTION

C-Glycosides, molecules bearing a carbohydrate unit appended to an aglycone or another carbohydrate through a C–C bond linkage, are ubiquitous in nature and are found to possess a myriad of biological activities, ranging from anticancer to antidiabetic properties.[1–3] Moreover, the robustness of *C*-glycosidic bonds toward hydrolytic enzymes *in vivo* has played a paramount role in the modern design of *C*-glycoside pharmaceutical candidates, as mimics or surrogates of the native *O*-glycosides.[4–6] A specific class of *C*-glycosides carrying an aliphatic motif on the anomeric carbon have featured prominently in various studies of biological functions and disease models,[5,7,8] as well as in the design of sugar-based therapeutics[9] (Scheme 1A). Of particular note, the synthesis of *C*-alkyl glycosides that are conjugated to amino acids[10–12] or peptide building blocks[13,14] offers a powerful platform to modify biologically active peptides of interest or to develop sugar-based peptidomimetics.[15,16] *C*-Glycosylated peptide analogs have proven to be more potent than their parent peptide molecules; yet, they simultaneously possess enhanced metabolic stability against peptidase degradation for drug delivery to the central nervous system.[15,17] As such, these glycosylated derivatives have been used to investigate the mechanism of blood brain transport, involving bioactive peptides and the role of glycosylation in stabilizing peptides in biological fluids and tissues.[15,17,18]

Notwithstanding the remarkable advances introduced for the stereoselective preparation of *C*-alkyl glycosides over the years, longstanding challenges remain to be addressed (Scheme 1B). One attractive approach to *C*-alkyl glycosides involves the generation of glycosyl radical[19,20] intermediates, which then engage with a

The bigger picture

C-Alkyl glycosides, especially those that are conjugated to amino acids or peptides, possess therapeutic properties and are important in biological studies as well as drug development programs. However, existing synthetic methods exhibit limited scope and often rely on impractical stoichiometric reagents. Catalytic regimes that promote glycosyl additions to less electrophilic acrylamides are typically inefficient. As described here, a Ti-catalyzed system has been devised to merge readily available glycosyl chlorides with activated alkenes, through stereocontrolled glycosyl radical addition, to furnish *C*-alkyl glycosides and glycopeptide conjugates with high anomeric selectivity. By utilizing alkynes as radical traps, access to *C*-alkenyl glycosides with *Z* olefins can be achieved. Mechanistic investigations provide insights to rationalize the observed reactivity profile of glycosyl chlorides, which are useful in the design of new catalytic reactions for complex carbohydrate synthesis.

second reactant to undergo stereocontrolled C–C bond formation under mild conditions. Inspired by Giese's seminal work involving glycosyl halide additions to activated olefins using tributyltin hydride under photolysis,[21,22] non-catalytic synthetic protocols often rely on a radical initiator (e.g., AIBN,[23] Et_3B/O_2,[24–27] and lauroyl peroxide[28,29]) in conjunction with stoichiometric quantities of a hydrogen atom donor to merge a variety of glycosyl precursors, some of which are specially designed,[19,20] with Michael acceptors. In one procedure, stoichiometric amounts of Et_3B/carbene-borane were utilized to mediate the addition of unprotected glycosyl radicals (from the corresponding glycosyl sulfoxides) to electron-deficient alkenes, including acrylamides.[27] In another instance, super-stoichiometric quantities of a pre-synthesized Ti(III) reagent was employed to promote additions of glycosyl bromides to activated olefins (20 equiv were used), but only four examples with $\leq$75% yields were reported.[30] Stoichiometric Ti(III) species has also been shown to reductively ring-open 1,2-anhydro sugars before trapping with electrophilic alkenes to give *C*-alkyl glycosides.[31] *C*-Allylation could also be accomplished by using allyltributylstannane in the presence of AIBN.[32] In a number of these reports, the scope of glycosyl units accessible is limited,[19,20] and application to complex carbohydrate synthesis is not demonstrated. Furthermore, the need for excess reagents reduces practicality and inadvertently produces waste that may pose complications, particularly if the compounds are toxic (e.g., organotin[19,20]) and/or pyrophoric (e.g., Et_3B[24–27]).

On the other hand, catalytic regimes that take advantage of transition metal[33–38] or photoredox[39–43] catalysis have been conceived to deliver *C*-alkyl glycosides. Still, methods that involved additions of glycosyl donors to alkenes suffer from limited scope. For example, the catalytic addition of nucleophilic glycosyl radicals to less electron-deficient acrylamide and its derivatives (versus acrylates) is generally inefficient, and undesired reduction by-products are formed instead.[33–43] In the absence of stoichiometric promoters,[27] access to important bioactive compounds or glycopeptide conjugates (cf. Scheme 1A), many of which could be potentially furnished through direct glycosyl delivery to an unsaturated amide moiety, consequently becomes an obstacle. Cross-coupling processes have been devised to generate *C*-alkyl glycosides, but existing reactions utilize air- and moisture-sensitive alkylmetal reagents, and poor stereoselectivity was observed for glucosides.[33] Similar to the non-catalytic reports, the diversity of glycoside scaffolds that can be afforded is unsatisfactory.

To address the aforementioned issues, we turned to nonprecious and non-toxic titanium catalysis, which has been demonstrated to generate alkyl radicals from the corresponding halides, driven by titanium's high affinity with halogen atoms.[44–51] We speculated if catalytic amounts of a Ti-based complex can be exploited to mediate the formation of glycosyl radicals from readily accessible and bench-stable glycosyl chloride donors, which can be prepared in high yield from their corresponding hemiacetals in one step.[52] Following diastereoselective radical addition to the activated alkene (or alkyne) and protonolysis with an appropriate proton source,[47] the corresponding *C*-alkyl glycoside (or *C*-alkenyl glycoside) may be obtained (Scheme 1C). To this end, we reasoned that a commercially available Ti(IV) complex could react with an inexpensive reducing agent to generate the requisite Ti(III) catalytic species that abstracts a Cl atom to give the glycosyl radical.[44–51] However, a number of challenges have to be overcome for the successful implementation of our conceived strategy: (1) Although Ti-mediated additions of carbogenic radicals to electron-deficient C=C bonds have been reported,[44–46,49,50] the corresponding intermolecular reactions with less electrophilic acrylamides or alkynes are scarce and typically low

[1]Department of Chemistry, National University of Singapore, 4 Science Drive 2, Singapore 117544, Republic of Singapore

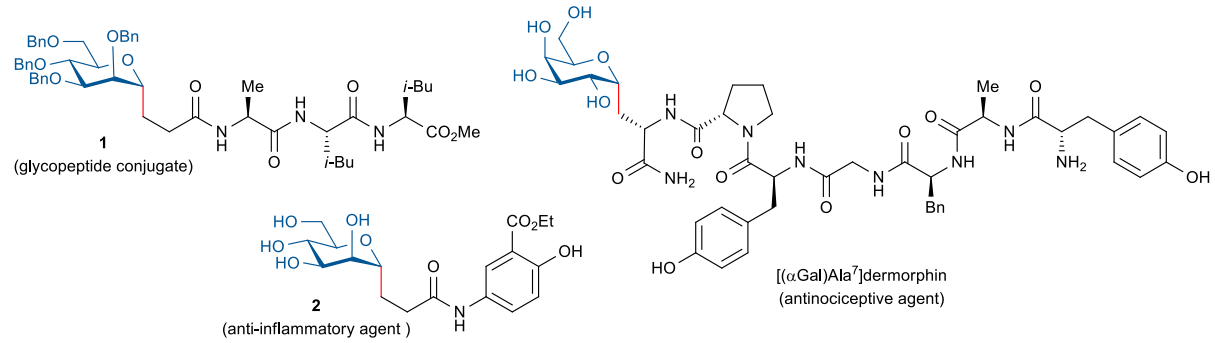
[2]Institute of High-Performance Computing, Agency for Science, Technology and Research (A*STAR), 1 Fusionopolis Way, #16-16 Connexis, Singapore 138632, Republic of Singapore

[3]Lead contact

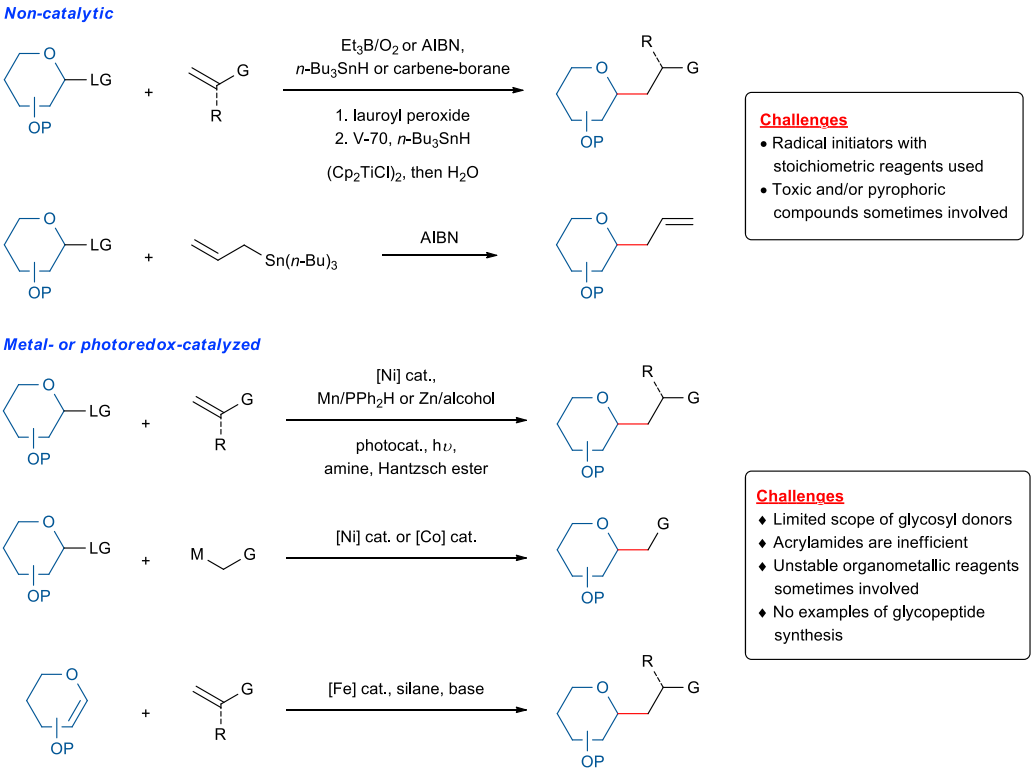
*Correspondence: chmqw@nus.edu.sg (Q.W.), zhang_xinglong@ihpc.a-star.edu.sg (X.Z.), chmkmj@nus.edu.sg (M.J.K.)

https://doi.org/10.1016/j.chempr.2021.09.008

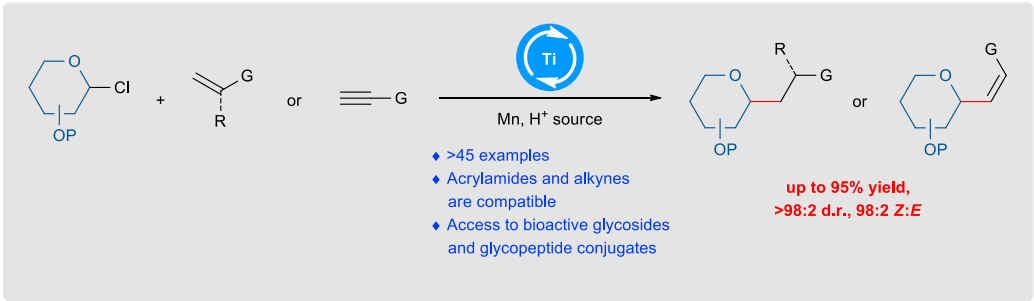
A The role of *C*-alkyl glycosides in biology and drug development



B Representative strategies to access *C*-alkyl glycosides via glycosyl radicals and their associated challenges

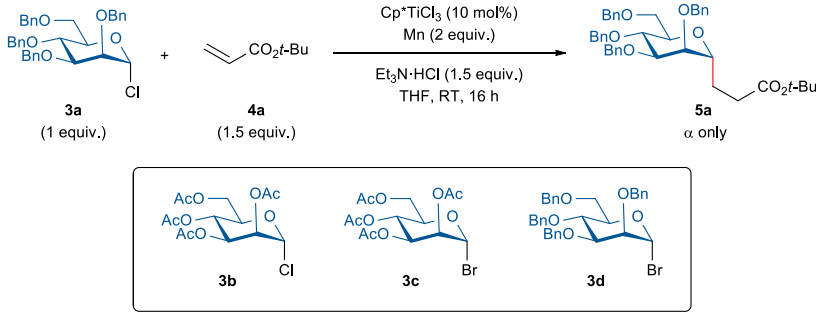


C This work: Ti-catalyzed glycosyl radical functionalization using glycosyl chlorides and activated alkenes/alkynes



Scheme 1. The motivation for developing a broadly applicable Ti-catalyzed regime to achieve stereoselective synthesis of *C*-glycosides

Table 1. Evaluation of reaction conditions



Entry	Deviation from standard conditions	Yield (%)[a]
1	none	93 (78)[b]
2	Zn instead of Mn	47
3	$CpTiCl_3$ instead of Cp^*TiCl_3	Trace
4	Cp_2TiCl_2 instead of Cp^*TiCl_3	80
5	DCM instead of THF	52
6	Toluene, DME, DMSO, or MeCN instead of THF	<10
7	2,4,6-Collidine·HCl instead of Et_3N·HCl	28
8	HCl (dioxane) instead of Et_3N·HCl	<10
9	*i*-PrOH, *t*-BuOH or Ph_2CHOH instead of Et_3N·HCl	Trace
10	H_2O instead of Et_3N·HCl	<2
11	**3b** instead of **3a**	<2
12[c]	**3c** instead of **3a**	40
13	**3d** instead of **3a**	48

Abbreviations: THF, tetrahydrofuran; DCM, dichloromethane; DME, dimethoxyethane; DMSO, dimethyl sulfoxide; RT, room temperature; Cp, cyclopentadienyl; Cp*, pentamethylcyclopentadienyl.
[a]Reactions were performed on 0.1 mmol scale. Yields are for isolated and purified products.
[b]The reaction was performed on 2 mmol scale. Value in parentheses denotes isolated yield.
[c]Glycal side product was obtained in 30% isolated yield in addition to the desired peracetylated *C*-alkyl glycoside.

yielding[49] or non-stereoselective.[44] (2) The involvement of polyhydroxy compounds, such as sugars, may potentially inhibit the catalytic reaction by competitive coordination to the oxophilic Ti center.[53] (3) The nucleophilic carbon-centered glycosyl radical may potentially associate with the electrophilic Ti complex, forming an alkyltitanium species that is susceptible to β-heteroatom elimination to give undesired glycal side products.[54,55] Thus, a new broadly applicable Ti-based catalytic system for carbohydrate synthesis remains to be identified. Herein, we disclose the first cases of a Ti-catalyzed manifold to facilitate stereoselective glycosyl radical functionalization using a wide range of glycosyl chlorides and activated alkenes/alkynes under mild reductive conditions.

RESULTS AND DISCUSSION

Reaction optimization

The model reaction of tetrabenzyl-protected α-mannosyl chloride **3a** (1 equiv) and acrylate **4a** (1.5 equiv) to afford *C*-alkyl glycoside **5a** was used to optimize conditions (Table 1). In the event, **5a** was secured in 93% yield as a single α-anomer, using 10 mol % of the commercially available Cp^*TiCl_3 (Cp^*: pentamethylcyclopentadienyl) with Mn (2 equiv) as reductant and Et_3N·HCl as proton donor in tetrahydrofuran (THF) at an ambient temperature (Table 1, entry 1). The reaction is highly robust

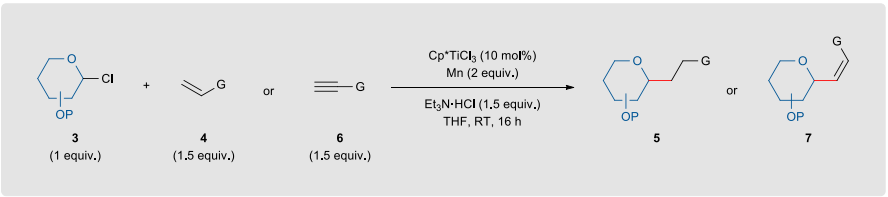
and could be carried out on a larger scale (2 mmol) to deliver **5a** in 78% yield. **5a** was isolated in lower yield (47%) when Mn was replaced with Zn (Table 1, entry 2). It merits mention that a color change (from red Ti(IV) to green Ti(III)) was detected in both Mn- and Zn-promoted reactions, suggesting that both reductants were capable of reducing Cp*$TiCl_3$ in THF.[47] Changing Cp*$TiCl_3$ to $CpTiCl_3$ or Cp_2TiCl_2 (Cp: cyclopentadienyl) led to diminished yields of **5a** (Table 1, entries 3 and 4). Switching THF to dichloromethane (DCM) generated **5a** in moderate yield (52%; Table 1, entry 5), but other solvents were much less effective (Table 1, entry 6).

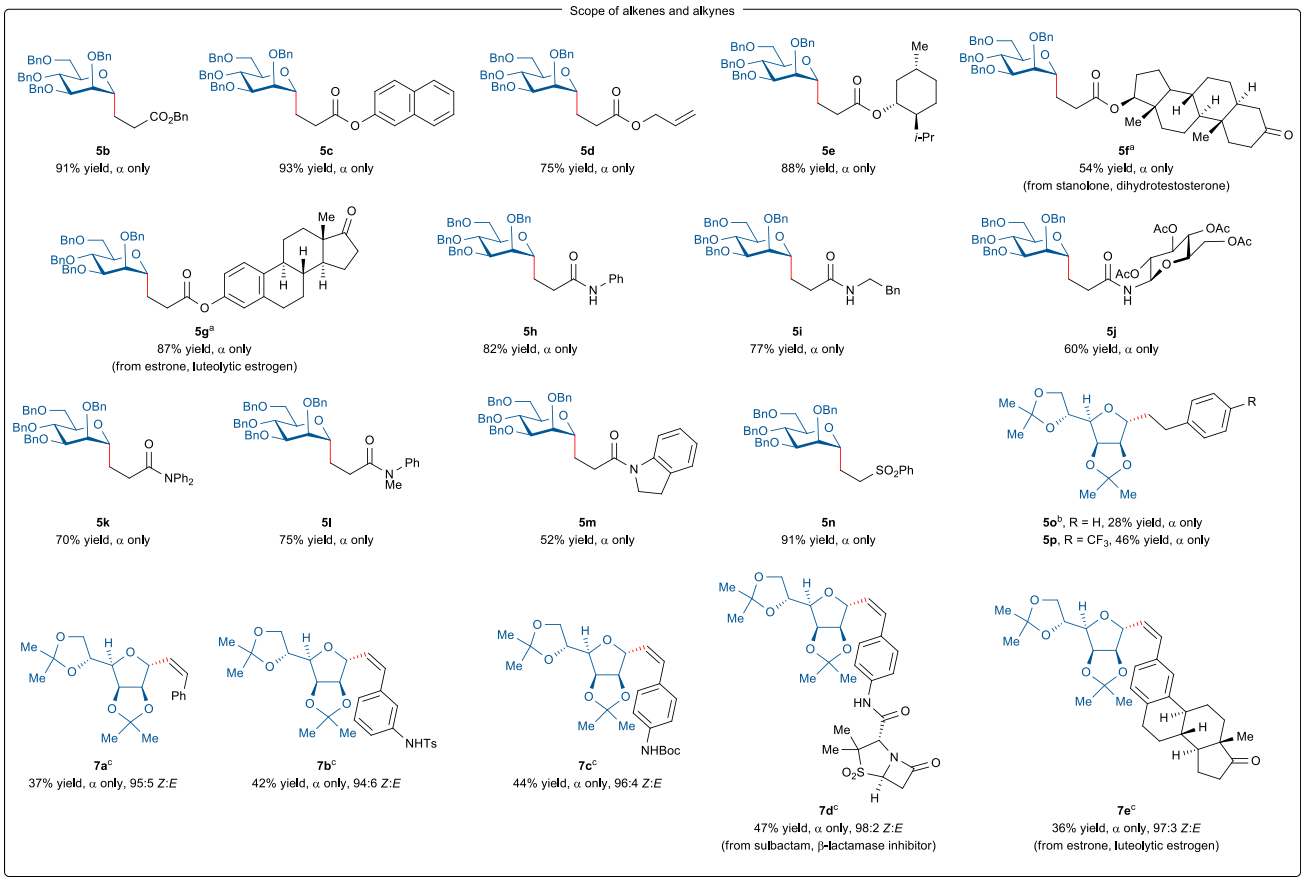
The identity of the proton source was crucial in the catalytic process. Changing $Et_3N{\cdot}HCl$ to 2,4,6-Collidine·HCl or HCl (dioxane) significantly lowered efficiency (Table 1, entries 7 and 8), whereas transformations with less Brønsted acidic alcohols or water were found to be unproductive (Table 1, entries 9 and 10). These observations may be attributed to the poor ability of the proton donor to induce protonolysis of the Ti–O bond[47] within the putative enolate intermediate, thus engendering inefficient catalytic turnover (see Scheme 7B for further discussion). The corresponding radical alkylations with other glycosyl precursors were also examined. Although mannosyl bromide **3d** could furnish **5a** in 48% yield under the established conditions (Table 1, entry 13), minimal reaction (<5% conv.) was detected using disarmed[56] tetraacetate mannosyl chloride **3b** (Table 1, entry 11), whereas **3c** afforded the desired *C*-alkyl glycoside in 40% yield along with 30% of glycal from undesired β-acetate elimination[54,55] of a putative glycosyltitanium species (Table 1, entry 12).

Reaction scope

Using **3a** or 2,3:5,6-di-*O*-isopropylidene D-mannofuranosyl chloride as the glycosyl donor, a variety of electronically activated alkenes **4** and alkynes **6** were examined under our established Ti-catalyzed conditions (Scheme 2). Remarkably, all products were obtained with exclusive α selectivity across the board. Reactions with acrylates derived from aliphatic alcohols (**5b**, **5d**, and **5e**) or phenols (**5c**), as well as complex enantioenriched bioactive compounds (**5f** and **5g**) containing electrophilic allylic carboxylate (**5d**) and ketone (**5f** and **5g**) motifs proceeded to deliver the desired adducts in 54%–91% yield. Gratifyingly, acrylamides bearing secondary and tertiary amides were amenable substrates in our catalytic regime, generating **5h–5m**, which includes an example derived from an aminoglycoside[57] (**5j**) in 52%–82% yield. Vinyl sulfone also underwent hydroalkylation to give **5n** in 91% yield, but transformations with the less electron-deficient styrenes afforded **5o** and **5p** in moderate yields (unactivated alkyl-substituted olefins were found to be non-productive).

To the best of our knowledge, terminal aryl alkynes were shown to be competent and selective glycosyl radical traps for the first time, affording *C*-glycosides **7a–7e** appended to a stereodefined *Z* olefin in 36%–47% yield and ≥94% *Z* selectivities (a previous report involving glycosyl radical addition to alkynes was poorly stereoselective and afforded *C*-glycosides bearing Te-substituted olefins[58]). For these cases, the more sizable Cp_2TiCl_2 proved to be optimal as Cp*$TiCl_3$ led to products with appreciably lower *Z* selectivities (see Scheme 7 for further discussion). Multifunctional glycosides containing Lewis basic and Lewis acidic sites (**7d** and **7e**) could be furnished, highlighting the present method's functional group compatibility. The *Z*:*E* stereochemical outcome may be rationalized by the minimization of steric repulsions between the C–glycosyl bond and the adjacent C–Ti bond, which are formed in an *anti*-configuration within the *in situ*-generated alkenyltitanium intermediate, analogous to previous observations in Ni[59] and Fe[60] catalytic manifolds (see Scheme 7B for further discussion). It is well documented that an *E*-to-*Z* switch in C=C bond geometry may give rise to beneficial enhancements in the properties





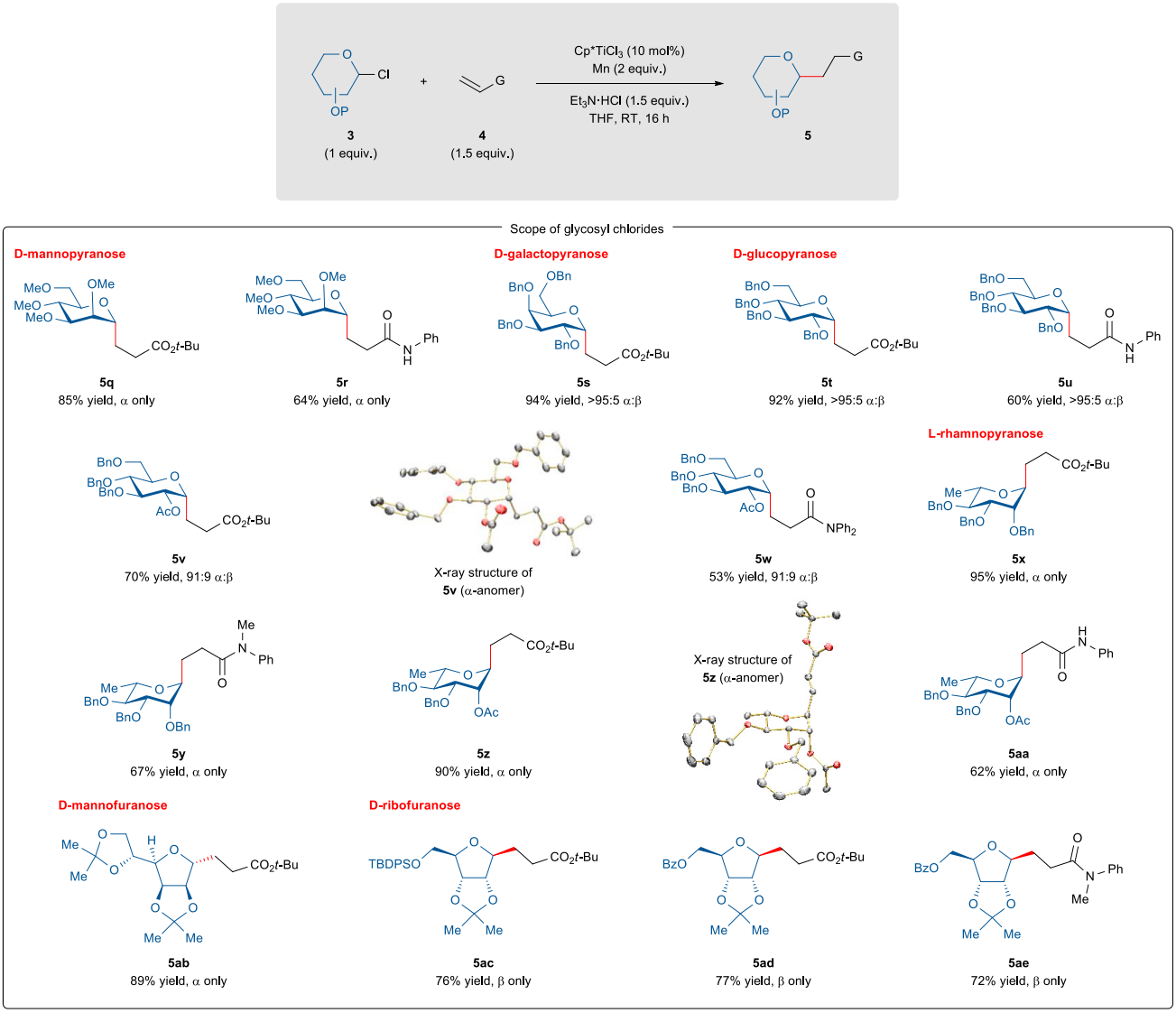
Scheme 2. The scope of alkenes and alkynes in Ti-catalyzed glycosyl radical functionalization

α:β ratios and *Z*:*E* ratios were determined by ^{1}H NMR analysis

Yields are for isolated and purified products. [a]The reactions were conducted with glycosyl donor (1.5 equiv) and alkene (1 equiv). [b]The reaction was conducted with alkene (10 equiv) and Cp_2TiCl_2 (10 mol %) as catalyst. [c]The reactions were conducted with glycosyl donor (2 equiv) and alkyne (1 equiv) with Cp_2TiCl_2 (10 mol %) as catalyst and EtOAc as solvent.

of a biologically active molecule.[61,62] Given that most reported *C*-alkenyl glycosides of medicinal value possess an *E* olefin moiety,[63–66] our catalytic protocol offers an attractive avenue to explore new chemical space in drug discovery through the stereoselective synthesis of *C*-glycoside analogs containing *Z* alkenes.

Reactions with methyl-protected D-mannopyranosyl chloride were similarly efficient under the standard conditions, giving **5q** and **5r** in 85% and 64% yield, respectively (Scheme 3). Besides mannosyl substrates, chloride donors of other classes of pyranoses and furanoses were also effective in glycosyl radical alkylation. Additions to acrylates and acrylamides were achieved with excellent diastereoselectivities in the presence of chlorides derived from D-galactopyranose (**5s**), D-glucopyranose (**5t–5w**), L-rhamnopyranose (**5x–5aa**), D-mannofuranose (**5ab**), and D-ribofuranose



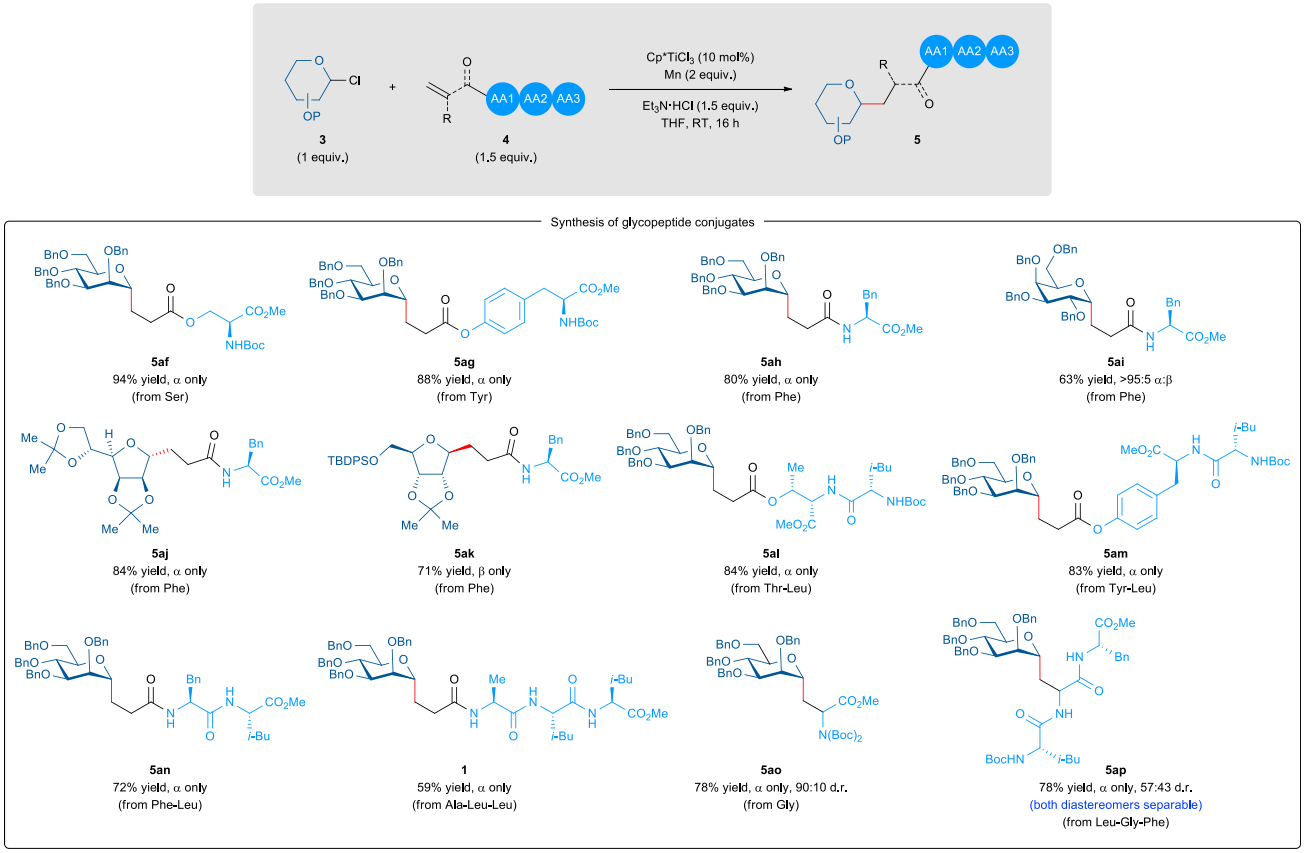
Scheme 3. The scope of carbohydrates in Ti-catalyzed glycosyl radical functionalization

α:β ratios were determined by ^{1}H NMR analysis. Yields are for isolated and purified products.

(**5ac–5ae**). The X-ray crystal structures of **5v** and **5z** confirmed the predominant formation of the α-anomer in each case. *C*-Alkyl glycosides with good α selectivities (**5v** and **5w**) were still generated even with a 2-acetyl-protected glucosyl chloride that is known to participate in neighboring group effects.[67]

Synthetic applications

To showcase the utility of our catalytic protocol in glycopeptide synthesis, acrylates as well as acrylamides conjugated to the side chain or N-terminus of α-amino acid and oligopeptide derivatives were merged with various glycosyl chlorides to furnish **5af–5ap** in 59%–94% yield with exceptional control of α/β anomeric selectivity (Scheme 4). These include *C*-alkyl glycosides bearing *O*-linked amino esters (**5af** and **5ag**) and dipeptides (**5al** and **5am**) as well as *N*-linked amino esters (**5ah–5ak**), dipeptides (**5an**), and tripeptides (**1**). The Ti-catalyzed strategy could also be extended to protected dehydroamino acid/peptide substrates to yield *C*-linked

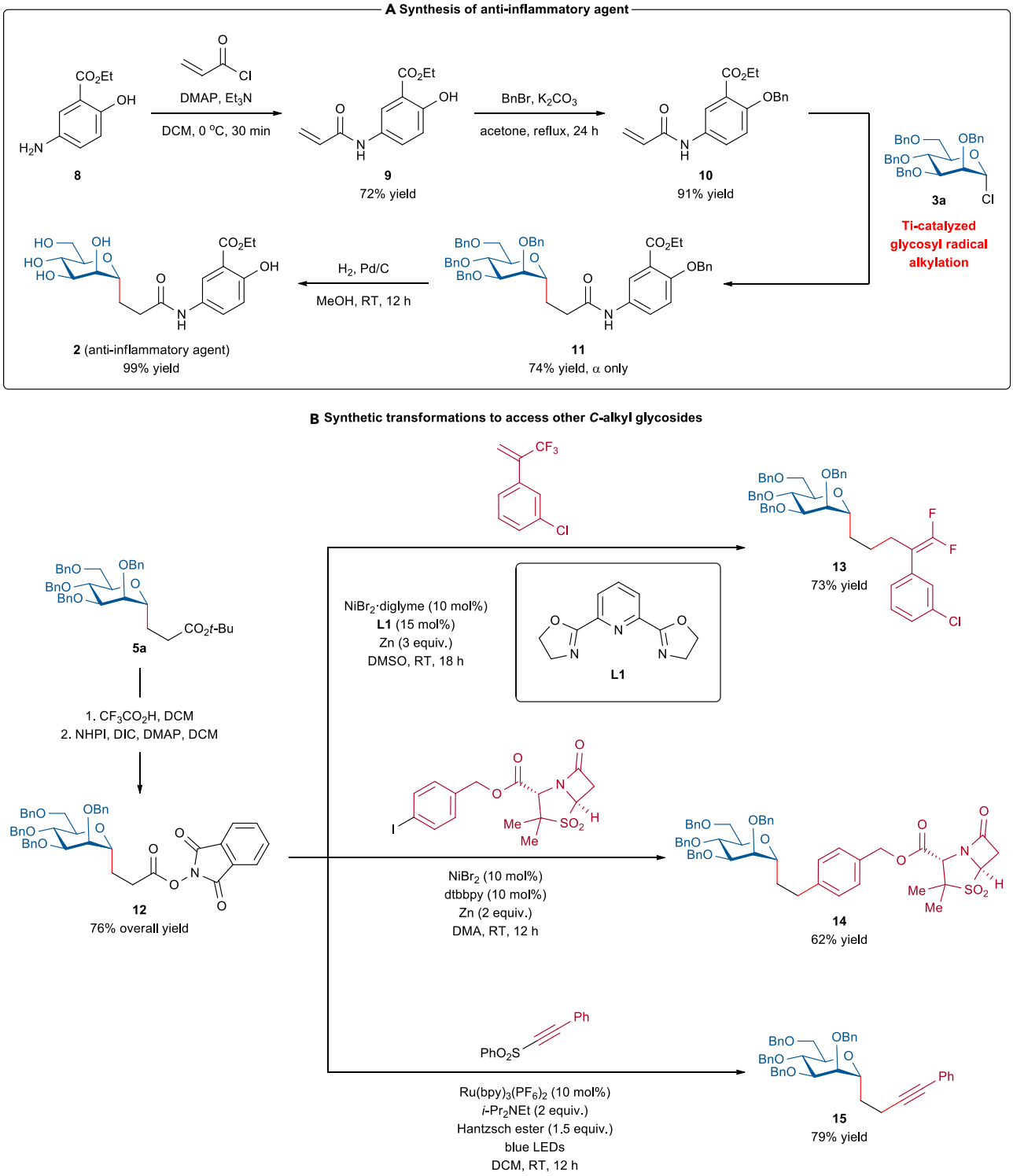


Scheme 4. Stereoselective synthesis of glycopeptide conjugates

α:β ratios and diastereomeric ratios (d.r.) were determined by ^{1}H NMR analysis. Yields are for isolated and purified products.

adducts with newly constructed *N*-substituted stereogenic centers (**5ao** and **5ap**). Whereas **5ao** was isolated in 90:10 diastereomeric ratio, the corresponding reaction leading to **5ap** was less diastereoselective. However, both diastereomers of **5ap** could be easily separated by simple silica gel flash column chromatography, allowing for potential compound screening studies. It is worth highlighting that past approaches to related *C*-linked glycosylated peptides, which are known to possess desirable medicinal attributes[15,17] (cf. Scheme 1A) were less practical, since excess toxic tributyltin hydride was used to induce glycosyl radical (generated from less stable glycosyl bromides) additions at elevated temperatures.[68]

In another application toward the concise assembly of anti-inflammatory agent **2**[69] (Scheme 5A), the known aminophenol **8** was subjected to a sequence of acetylation and benzylation to form acrylamide **10** in 66% overall yield. This sets the stage for the key Ti-catalyzed coupling with **3a** to afford *C*-alkyl glycoside **11** in 74% yield and complete α selectivity, before a final benzyl ether deprotection furnished **2** in 99% yield. In addition to bioactive molecule synthesis, versatile sugar building blocks bearing a carboxylic ester functionality, such as **5a**, could be readily modified by a series of synthetic transformations to generate molecular diversity (Scheme 5B). Conversion of **5a** to its redox-active ester-variant **12** followed by established catalytic decarboxylative C–C bond forming reactions provide convenient entry to a wider set of prized carbohydrates. For example, Ni-catalyzed defluorinative alkylation[70] and arylation[71] gave functionalized *C*-alkyl glycosides **13** and **14** in 73%



Scheme 5. Stereoselective synthesis of bioactive C-alkyl glycosides and other derivatives

α:β ratios were determined by ^{1}H NMR analysis. Yields are for isolated and purified products.

and 62% yield, respectively. On the other hand, **15** was formed in 79% yield through photoredox-catalyzed decarboxylative alkynylation[72] under blue light irradiation.

Mechanistic investigations

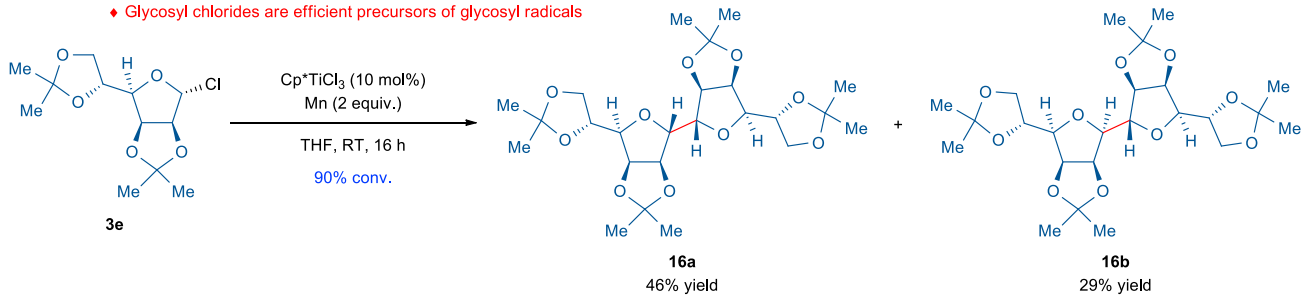
A series of control experiments were performed to gain more insights into the mechanism of the developed Ti-catalyzed reactions (Scheme 6). Support for the generation of glycosyl radical intermediates from the chloride substrates was obtained by subjecting **3e** to the standard conditions in the absence of the alkene/alkyne acceptor, which generated a mixture of diastereomeric radical homocoupling products[73] **16a** and **16b** in 46% and 29% yield, respectively (Scheme 6A).

In another set of deuterium labeling experiments to probe the origin of the hydrogen source (Scheme 6B), the reaction of **3e** with **4a** using d_8-THF as solvent was found to give the expected α-anomer product **5ab** in 47% yield with <5% deuterium incorporation, suggesting that any hydrogen atom transfer with THF is negligible. On the other hand, using $Et_3N{\cdot}DCl$ as the deuteron source, **3e** underwent Ti-catalyzed glycosyl radical alkylation with **4a** to give *d*-**5ab** in 85% yield with 81% deuterium incorporated at the α-carbonyl site, along with 5% yield of the reduced glycosyl side product **17**. In similar fashion, treating **3e** with phenylacetylene **6a** in the presence of $Et_3N{\cdot}DCl$ afforded *d*-**7a** as a single *Z* isomer in 24% yield with 64% deuterium incorporation, as well as appreciable amounts of **17**. The incomplete deuteration in both cases likely stems from adventitious formation of $Et_3N{\cdot}HCl$ from $Et_3N{\cdot}DCl$ and trace moisture in THF, consequently giving rise to competitive protonation.

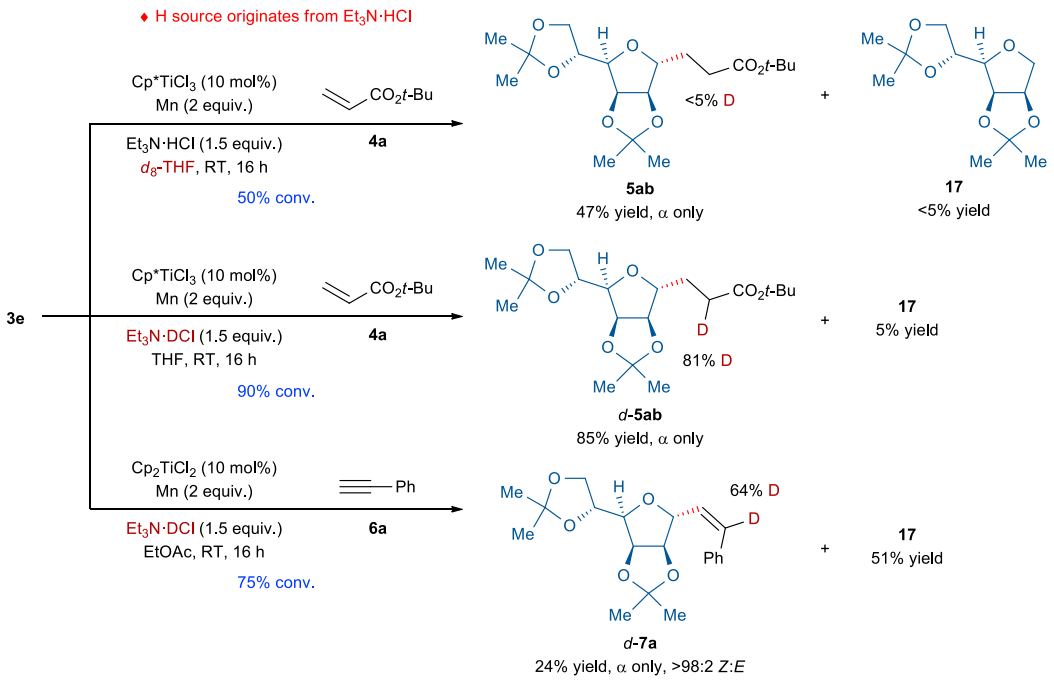
The remarkable efficiency of glycosyl radical additions to acrylamides (Schemes 2, 3, and 4) led us to wonder if nucleophilic glycosyl radicals are uniquely reactive for such C–C bond forming transformations. Specifically, we questioned how reactive would glycosyl chlorides compare with tertiary alkyl chlorides, since both classes of organochlorides could be activated under Ti catalysis. Prior to our study, the relative thermodynamic stability of tertiary alkyl radicals and glycosyl radicals is unclear. Although tertiary alkyl radicals are known to participate readily in Ti-catalyzed radical alkylation of electron-poor alkenes,[46,49,50] reactions with less electrophilic substrates, such as acrylamides, are significantly less efficient.[46,49] This is underscored by the control experiments in Scheme 6C, where the union of tertiary chloroalkane **18** and acrylate **4a** gave **19a** in 92% yield. In stark contrast, the reaction between **18** and acrylamide **4b** only afforded **19b** in 18% yield (<5% using conditions from a previous protocol[46]). The significantly lower conversion of **18** in the presence of the more electron-rich **4b** (versus **4a**) suggest that **4b** may competitively associate with a putative Ti complex to inhibit coordination and activation of **18** (see below for further discussion).

Competition experiments using a 1:1 mixture of α-mannosyl chloride **3a** and **18** further showcase the distinct reactivity difference between the two substrates. Under our established Ti-catalyzed conditions in the presence of **4a** or **4b**, **3a** outcompeted **18** and preferentially underwent addition to yield the desired products **5a** and **5h** in 63%–72% yield. The origin of the unexpected difference in reactivity between glycosyl chlorides and tertiary chloroalkanes is elucidated through density functional theory (DFT) calculations (see section S7 for full computational details). As shown in Scheme 7A, using mannosyl chloride **3f** and *t*-butyl chloride **20** as model systems, the bond strengths of the C–Cl bond were found to be similar in both cases (bond dissociation enthalpy [BDE] = 80.4 and 80.3 kcal mol^{-1}, respectively), suggesting similar C–Cl bond strengths for homolytic cleavage in both mannosyl and *tert*-butyl chloride. However, in the presence of the active Cp^*TiCl_2 species (generated from *in*

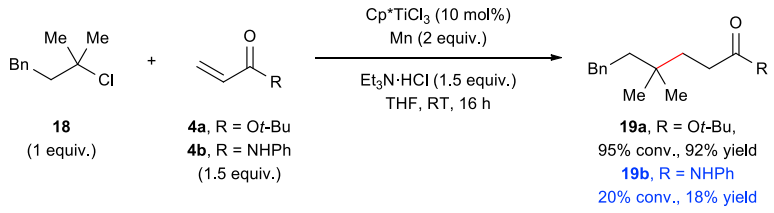
A Radical homocoupling experiment

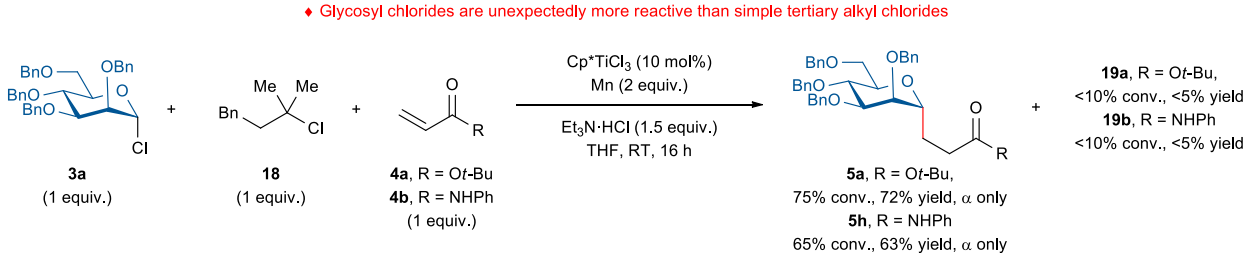


B Deuterium labelling studies



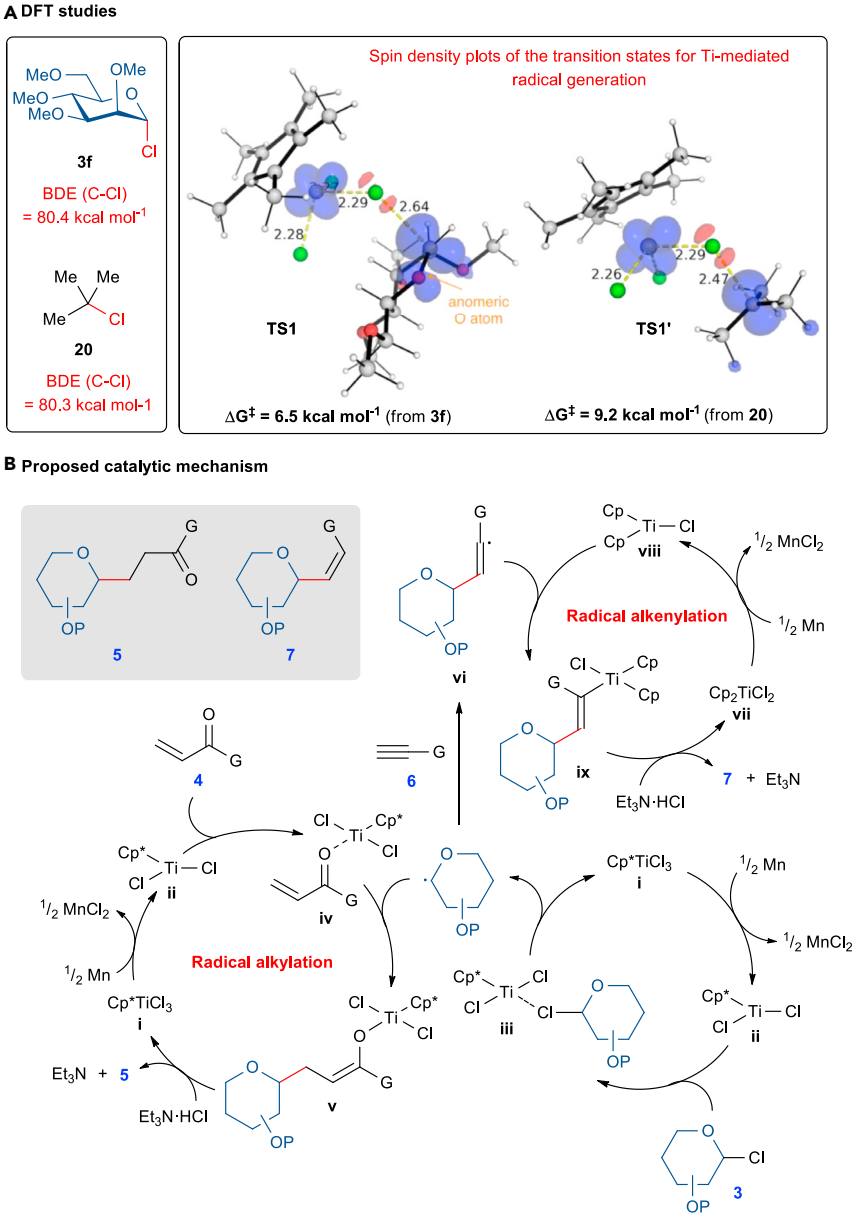
C Competition experiments





Scheme 6. Mechanistic studies

α:β ratios and *Z*:*E* ratios were determined by ^{1}H NMR analysis. Yields are for isolated and purified products.



Scheme 7. Computational studies and proposed mechanism for Ti-catalyzed glycosyl radical functionalization

All Gibbs energies were computed at the SMD(THF)-B3LYP-D3BJ/def2-TZVP//B3LYP-D3BJ/def2-SVP level of theory. Key bond distances for the transition states are given in Å.

situ reduction of Cp*$TiCl_3$), the energy barrier for the formation of mannosyl radical (most stable chair-like conformation[23,74]) was computed to be 2.7 kcal mol^{-1} lower than that for the formation of *tert*-butyl radical. This translates to a kinetic preference for the generation of mannosyl radical over *tert*-butyl radical by ~95 times at ambient temperature using simple transition-state theory. Overall, the Ti-mediated radical formation step was revealed to be rate determining, exergonic, and irreversible, as the subsequent mannosyl radical addition to the Lewis acidic Cp*$TiCl_2$-activated acrylamide **4b** proceeds with negligible barrier (see section S7.4 for details). Without Ti participation, the barrier for direct mannosyl radical conjugate addition

becomes appreciably higher and is rate determining (see section S7.3 for details). In contrast to the reactions with tertiary alkyl chlorides (Scheme 6C), it is worth mentioning that glycosyl chlorides are more capable of competing effectively with **4b** for coordination to the active Ti(III) center species to trigger C–Cl bond cleavage (see DFT-binding thermodynamics calculations in section S7.6).

Analysis of the spin densities of the transition states for radical formation (Scheme 7A) as well as those of the radical intermediates provides a possible rationale for the more favorable formation of mannosyl radical (versus *tert*-butyl radical). The spin density in **TS1** is localized on the anomeric carbon as well as on the anomeric oxygen. On the other hand, **TS1′** has spin density largely on the carbon atom from which the chlorine is abstracted. The stabilization of the radical character by the anomeric oxygen in **TS1** likely contributes to stabilization of the structure, resulting in a lower activation barrier than the formation of *tert*-butyl radical via **TS1′**. To summarize, our DFT studies shed light on the crucial role of the Ti-based catalytic species in accelerating glycosyl radical generation as well as glycosyl radical addition across the C–C π-bond, thus facilitating efficient alkylations of less activated acrylamides.

A plausible mechanism for the Ti-catalyzed glycosyl radical functionalization is proposed in Scheme 7B. Direct single-electron reduction of Cp^*TiCl_3 (**i**) by Mn[47] in THF affords the active monomeric Ti(III) complex **ii** that subsequently abstracts a Cl atom from glycosyl chloride **3** to generate the putative glycosyl radical intermediate. An outer-sphere single-electron reduction mechanism can be excluded from cyclic voltammetry studies[46] (see section S6.4 for details). In the presence of an electrophilic olefin **4** (presumably coordinated to another molecule of **ii** via carbonyl group[75,76]), glycosyl radical addition occurs selectively from the sterically less hindered face, forming a second radical that undergoes facile reduction and association with **ii** to give titanium enolate **v**.[30] Finally, protonolysis of the Ti–O bond with $Et_3N{\cdot}HCl$ releases the desired *C*-alkyl glycoside **5** and regenerates **i**.

On the other hand, when alkyne **6** is involved, glycosyl radical addition across the C–C triple bond is postulated to proceed to give a nascent resonance-stabilized π-type alkenyl radical **vi**.[60] **vi** then gets trapped by a molecule of **viii** (obtained from reduction of Cp_2TiCl_2 [**vii**]) to furnish a configurationally defined intermediate **ix** in which the C–glycosyl bond and the adjacent C–Ti bond are oriented in *anti*-fashion to avoid steric clash between the sizable glycosyl group and the organotitanium species. As highlighted earlier, use of the sterically more encumbered **vii** (versus **i**) engenders greater steric repulsions with the glycosyl substituent in the corresponding alkenyltitanium species to ensure maximal *Z* selectivity. The ensuing stereoretentive protonolysis with $Et_3N{\cdot}HCl$ selectively affords the *C*-alkenyl glycoside **7** bearing a *Z* olefin. Alternatively, Ti→Mn exchange with $MnCl_2$ (by-product derived from Mn oxidation) followed by protonolysis of the resulting alkenylmanganese intermediate cannot be entirely excluded.[60,77]

Conclusion

Starting from easily accessible and convenient-to-use glycosyl chlorides, we have shown that a Ti-based catalyst can effectively promote the formation of glycosyl radicals that undergo addition to activated alkenes and alkynes with excellent control of α/β anomeric and *Z*:*E* selectivity at ambient temperature under reductive conditions. Notably, the use of $Et_3N{\cdot}HCl$ allows for efficient protonolysis of the organotitanium intermediate to turn over the catalytic cycle, thus overcoming the requirement for stoichiometric Ti-based reagents in previous disclosures. On the basis of the operational ease as well as applicability to complex sugar and glycopeptide synthesis,

we expect the present catalytic manifold to find extensive use in carbohydrate research and facilitate medicinal chemistry initiatives toward the development of glyco-based therapeutic candidates.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Ming Joo Koh (chmkmj@nus.edu.sg).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

The X-ray crystal structure data files for **5v** and **5z** have been deposited with the Cambridge Crystallographic Data Centre under accession numbers CCDC: 2080693 and 2080694. Geometries of all DFT-optimized structures have been uploaded to zenodo.org under open access (https://doi.org/10.5281/zenodo.4876297).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2021.09.008.

ACKNOWLEDGMENTS

This research was supported by the Ministry of Education of Singapore Academic Research Funds Tier 1: R-143-000-B57-114 and R-143-000-B65-114 (M.J.K.) and the Institute of High-Performance Computing, A*STAR (X.Z.). X.Z. acknowledges the A*STAR Computational Resource Centre (A*CRC) of Singapore for the use of its high-performance computing facilities. We thank Ms. Geok Kheng Tan for X-ray crystallographic analysis.

AUTHOR CONTRIBUTIONS

Y.J. and Q.W. developed the catalytic method. X.Z. carried out the DFT calculations. M.J.K. directed the investigations and wrote the manuscript with revisions provided by the other authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: June 9, 2021
Revised: August 15, 2021
Accepted: September 16, 2021
Published: October 12, 2021

REFERENCES

1. Hultin, P.G. (2005). Bioactive *C*-glycosides from bacterial secondary metabolism. Curr. Top. Med. Chem. *5*, 1299–1331.

2. Kitamura, K., Ando, Y., Matsumoto, T., and Suzuki, K. (2018). Total synthesis of aryl *C*-glycoside natural products: strategies and tactics. Chem. Rev. *118*, 1495–1598.

3. Liao, H., Ma, J., Yao, H., and Liu, X.-W. (2018). Recent progress of *C*-glycosylation methods in the total synthesis of natural products and pharmaceuticals. Org. Biomol. Chem. *16*, 1791–1806.

4. Kuberan, B., Sikkander, S.A., Tomiyama, H., and Linhardt, R.J. (2003). Synthesis of a *C*-glycoside analogue of sTn: an HIV- and

tumor-associated antigen. Angew. Chem. Int. Ed. Engl. *42*, 2073–2075.

5. Yang, G., Schmieg, J., Tsuji, M., and Franck, R.W. (2004). The *C*-glycoside analogue of the immunostimulant α-galactosylceramide (KRN7000): synthesis and striking enhancement of activity. Angew. Chem. Int. Ed. Engl. *43*, 3818–3822.

6. Bokor, É., Kun, S., Goyard, D., Tóth, M., Praly, J.-P., Vidal, S., and Somsák, L. (2017). *C*-glycopyranosyl arenes and hetarenes: synthetic methods and bioactivity focused on antidiabetic potential. Chem. Rev. *117*, 1687–1764.

7. Peri, F., Cipolla, L., Rescigno, M., La Ferla, B., and Nicotra, F. (2001). Synthesis and biological evaluation of an anticancer vaccine containing the *C*-glycoside analogue of the tn epitope. Bioconjug. Chem. *12*, 325–328.

8. Hakulinen, J.K., Hering, J., Brändén, G., Chen, H., Snijder, A., Ek, M., and Johansson, P. (2017). MraY–antibiotic complex reveals details of tunicamycin mode of action. Nat. Chem. Biol. *13*, 265–267.

9. Schmieg, J., Yang, G., Franck, R.W., and Tsuji, M. (2003). Superior protection against malaria and melanoma metastases by a *C*-glycoside analogue of the natural killer T cell ligand α-galactosylceramide. J. Exp. Med. *198*, 1631–1641.

10. Lash, L.L., Sanders, J.M., Akiyama, N., Shoji, M., Postila, P., Pentikäinen, O.T., Sasaki, M., Sakai, R., and Swanson, G.T. (2008). Novel analogs and stereoisomers of the marine toxin neodysiherbaine with specificity for kainate receptors. J. Pharmacol. Exp. Ther. *324*, 484–496.

11. Richard, M., Chateau, A., Jelsch, C., Didierjean, C., Manival, X., Charron, C., Maigret, B., Barberi-Heyob, M., Chapleur, Y., Boura, C., and Pellegrini-Moïse, N. (2016). Carbohydrate-based peptidomimetics targeting neuropilin-1: synthesis, molecular docking study and in vitro biological activities. Bioorg. Med. Chem. *24*, 5315–5325.

12. Hogervorst, T.P., Li, R.J.E., Marino, L., Bruijns, S.C.M., Meeuwenoord, N.J., Filippov, D.V., Overkleeft, H.S., van der Marel, G.A., van Vliet, S.J., van Kooyk, Y., and Codée, J.D.C. (2020). *C*-mannosyl lysine for solid phase assembly of mannosylated peptide conjugate cancer vaccines. ACS Chem. Biol. *15*, 728–739.

13. Gobbo, M., Biondi, L., Filira, F., Gennaro, R., Benincasa, M., Scolaro, B., and Rocchi, R. (2002). Antimicrobial peptides: synthesis and antibacterial activity of linear and cyclic drosocin and apidaecin 1b analogues. J. Med. Chem. *45*, 4494–4504.

14. Aljohani, S., Hussein, W.M., Toth, I., and Simerska, P. (2019). Carbohydrates in vaccine development. Curr. Drug Deliv. *16*, 609–617.

15. Negri, L., Lattanzi, R., Tabacco, F., Scolaro, B., and Rocchi, R. (1998). Glycodermorphins: opioid peptides with potent and prolonged analgesic activity and enhanced blood-brain barrier penetration. Br. J. Pharmacol. *124*, 1516–1522.

16. Chapman, T.M., Davies, I.G., Gu, B., Block, T.M., Scopes, D.I.C., Hay, P.A., Courtney, S.M., McNeill, L.A., Schofield, C.J., and Davis, B.G. (2005). Glyco- and peptidomimetics from three-component Joullié–Ugi coupling show selective antiviral activity. J. Am. Chem. Soc. *127*, 506–507.

17. Negri, L., Lattanzi, R., Tabacco, F., Orrù, L., Severini, C., Scolaro, B., and Rocchi, R. (1999). Dermorphin and deltorphin glycosylated analogues: synthesis and antinociceptive activity after systemic administration. J. Med. Chem. *42*, 400–404.

18. Polt, R., Porreca, F., Szabò, L.Z., Bilsky, E.J., Davis, P., Abbruscato, T.J., Davis, T.P., Harvath, R., Yamamura, H.I., and Hruby, V.J. (1994). Glycopeptide enkephalin analogues produce analgesia in mice: evidence for penetration of the blood-brain barrier. Proc. Natl. Acad. Sci. USA *91*, 7114–7118.

19. Yang, Y., and Yu, B. (2017). Recent advances in the chemical synthesis of *C*-glycosides. Chem. Rev. *117*, 12281–12356.

20. Xu, L.-Y., Fan, N.-L., and Hu, X.-G. (2020). Recent development in the synthesis of *C*-glycosides involving glycosyl radicals. Org. Biomol. Chem. *18*, 5095–5109.

21. Giese, B., and Dupuis, J. (1983). Diastereoselective syntheses of *C*-glycopyranosides. Angew. Chem. Int. Ed. Engl. *22*, 622–623.

22. Giese, B., Dupuis, J., Leising, M., Nix, M., and Lindner, H.J. (1987). Synthesis of *C*-pento, -hexo-, and -heptulo-pyranosyl compounds via radical C–C bond-formation reactions. Carbohydr. Res. *171*, 329–341.

23. Abe, H., Shuto, S., and Matsuda, A. (2001). Highly α- and β-selective radical *C*-glycosylation reactions using a controlling anomeric effect based on the conformational restriction strategy. a study on the conformation–anomeric effect–stereoselectivity relationship in anomeric radical reactions. J. Am. Chem. Soc. *123*, 11870–11882.

24. Guindon, Y., Bencheqroun, M., and Bouzide, A. (2005). Synthesis of postulated Molecular Probes: stereoselective free-radical-mediated *C*-glycosylation in tandem with hydrogen transfer. J. Am. Chem. Soc. *127*, 554–558.

25. Inoue, M. (2017). Evolution of radical-based convergent strategies for total syntheses of densely oxygenated natural products. Acc. Chem. Res. *50*, 460–464.

26. Masuda, K., Nagatomo, M., and Inoue, M. (2017). Direct assembly of multiply oxygenated carbon chains by decarbonylative radical-radical coupling reactions. Nat. Chem. *9*, 207–212.

27. Shang, W., Su, S.-N., Shi, R., Mou, Z.-D., Yu, G.-Q., Zhang, X., and Niu, D. (2021). Generation of glycosyl radicals from glycosyl sulfoxides and its use in the synthesis of C-linked glycoconjugates. Angew. Chem. Int. Ed. Engl. *60*, 385–390.

28. Kiya, N., Hidaka, Y., Usui, K., and Hirai, G. (2019). Synthesis of CH_2-linked α(1,6)-disaccharide analogues by α-selective radical coupling *C*-glycosylation. Org. Lett. *21*, 1588–1592.

29. Hidaka, Y., Kiya, N., Yoritate, M., Usui, K., and Hirai, G. (2020). Synthesis of CH_2-linked α-galactosylceramide and its glucose analogues through glycosyl radical-mediated direct *C*-glycosylation. Chem. Commun. (Camb) *56*, 4712–4715.

30. Spencer, R.P., and Schwartz, J. (1997). Titanium(III)-promoted stereoselective synthesis of simple *C*-glycosides. J. Org. Chem. *62*, 4204–4205.

31. Parrish, J.D., and Little, R.D. (2002). Preparation of α-*C*-glycosides from glycals. Org. Lett. *4*, 1439–1442.

32. Manabe, S., Aihara, Y., and Ito, Y. (2011). Radical *C*-glycosylation reaction of pyranosides with the 2,3-trans carbamate group. Chem. Commun. (Camb) *47*, 9720–9722.

33. Gong, H., and Gagné, M.R. (2008). Diastereoselective Ni-catalyzed Negishi cross-coupling approach to saturated, fully oxygenated *C*-alkyl and *C*-aryl glycosides. J. Am. Chem. Soc. *130*, 12177–12183.

34. Gong, H., Andrews, R.S., Zuccarello, J.L., Lee, S.J., and Gagné, M.R. (2009). Sn-free Ni-catalyzed reductive coupling of glycosyl bromides with activated alkenes. Org. Lett. *11*, 879–882.

35. McKay, M.J., and Nguyen, H.M. (2012). Recent advances in transition metal-catalyzed glycosylation. ACS Catal. *2*, 1563–1595.

36. Zeng, J., Ma, J., Xiang, S., Cai, S., and Liu, X.-W. (2013). Stereoselective β-*C*-glycosylation by a palladium-catalyzed decarboxylative allylation: formal synthesis of aspergillide A. Angew. Chem. Int. Ed. Engl. *52*, 5134–5137.

37. Tardieu, D., Desnoyers, M., Laye, C., Hazelard, D., Kern, N., and Compain, P. (2019). Stereoselective synthesis of *C*,*C*-glycosides from exo-glycals enabled by iron-mediated hydrogen atom transfer. Org. Lett. *21*, 7262–7267.

38. Zhu, F., and Walczak, M.A. (2020). Stereochemistry of transition metal complexes controlled by the metallo-anomeric effect. J. Am. Chem. Soc. *142*, 15127–15136.

39. Andrews, R.S., Becker, J.J., and Gagné, M.R. (2010). Intermolecular addition of glycosyl halides to alkenes mediated by visible light. Angew. Chem. Int. Ed. Engl. *49*, 7274–7276.

40. Andrews, R.S., Becker, J.J., and Gagné, M.R. (2011). Investigating the rate of photoreductive glucosyl radical generation. Org. Lett. *13*, 2406–2409.

41. Andrews, R.S., Becker, J.J., and Gagné, M.R. (2012). A photoflow reactor for the continuous photoredox-mediated synthesis of *C*-glycoamino acids and *C*-glycolipids. Angew. Chem. Int. Ed. Engl. *51*, 4140–4143.

42. Wan, I.C.S., Witte, M.D., and Minnaard, A.J. (2019). From *d*- to *l*-monosaccharide derivatives via photodecarboxylation-alkylation. Org. Lett. *21*, 7669–7673.

43. Ji, P., Zhang, Y., Dong, Y., Huang, H., Wei, Y., and Wang, W. (2020). Synthesis of enantioenriched α-deuterated α-amino acids enabled by an Organophotocatalytic radical approach. Org. Lett. *22*, 1557–1562.

44. Zheng, X., Dai, X.-J., Yuan, H.-Q., Ye, C.-X., Ma, J., and Huang, P.-Q. (2013). Umpolung of hemiaminals: titanocene-catalyzed dehydroxylative radical coupling reactions with activated alkenes. Angew. Chem. Int. Ed. Engl. *52*, 3494–3498.

45. Zheng, X., He, J., Li, H.-H., Wang, A., Dai, X.-J., Wang, A.-E., and Huang, P.-Q. (2015). Titanocene(III)-catalyzed three-component reaction of secondary amides, aldehydes, and electrophilic alkenes. Angew. Chem. Int. Ed. Engl. *54*, 13739–13742.

46. Wu, X., Hao, W., Ye, K.-Y., Jiang, B., Pombar, G., Song, Z., and Lin, S. (2018). Ti-catalyzed radical alkylation of secondary and tertiary alkyl chlorides using Michael acceptors. J. Am. Chem. Soc. *140*, 14836–14843.

47. McCallum, T., Wu, X., and Lin, S. (2019). Recent advances in titanium radical redox catalysis. J. Org. Chem. *84*, 14369–14380.

48. Gualandi, A., Calogero, F., Mazzarini, M., Guazzi, S., Fermi, A., Bergamini, G., et al. (2020). Cp_2TiCl_2-catalyzed photoredox allylation of aldehydes with visible light. ACS Catal. *10*, 3857–3863.

49. Xie, H., Guo, J., Wang, Y.-Q., Wang, K., Guo, P., Su, P.-F., Wang, X., and Shu, X.-Z. (2020). Radical Dehydroxylative alkylation of tertiary alcohols by Ti catalysis. J. Am. Chem. Soc. *142*, 16787–16794.

50. Li, F., Lin, S., Chen, Y., Shi, C., Yan, H., Li, C., Wu, C., Lin, L., Duan, C., and Shi, L. (2021). Photocatalytic generation of π-Allyltitanium complexes via radical intermediates. Angew. Chem. Int. Ed. Engl. *60*, 1561–1566.

51. Wang, X., Cui, P., Xia, C., and Wu, L. (2021). Catalytic boration of alkyl halides with borane without hydrodehalogenation enabled by titanium catalyst. Angew. Chem. Int. Ed. Engl. *60*, 12298–12303.

52. Wang, Q., An, S., Deng, Z., Zhu, W., Huang, Z., He, G., and Chen, G. (2019). Palladium-catalysed C–H glycosylation for synthesis of *C*-aryl glycosides. Nat. Catal. *2*, 793–800.

53. Notestein, J.M., Andrini, L.R., Kalchenko, V.I., Requejo, F.G., Katz, A., and Iglesia, E. (2007). Structural assessment and catalytic consequences of the oxygen coordination environment in grafted Ti–calixarenes. J. Am. Chem. Soc. *129*, 1122–1131.

54. Cavallaro, C.L., and Schwartz, J. (1995). A rapid synthesis of pyranoid glycals from glycosyl bromides. J. Org. Chem. *60*, 7055–7057.

55. Spencer, R.P., Cavallaro, C.L., and Schwartz, J. (1999). Rapid preparation of variously protected glycals using titanium(III). J. Org. Chem. *64*, 3987–3995.

56. Fraser-Reid, B., and López, J.C. (2011). Armed–disarmed effects in carbohydrate chemistry: history, synthetic and mechanistic studies. In Reactivity Tuning in Oligosaccharide Assembly, B. Fraser-Reid and J.C. López, eds. (Springer), pp. 1–29.

57. Magnet, S., and Blanchard, J.S. (2005). Molecular insights into aminoglycoside action and resistance. Chem. Rev. *105*, 477–498.

58. Yamago, S., Miyazoe, H., and Yoshida, J.-i. (1999). Synthesis of vinylic *C*-glycosides from telluroglycosides. Addition of photochemically and thermally generated glycosyl radicals to alkynes. Tetrahedron Lett. *40*, 2343–2346.

59. Jiang, Y., Pan, J., Yang, T., Zhao, Y., and Koh, M.J. (2021). Nickel-catalyzed site- and stereoselective reductive alkylalkynylation of alkynes. Chem *7*, 993–1005.

60. Cheung, C.W., Zhurkin, F.E., and Hu, X. (2015). *Z*-selective olefin synthesis via iron-catalyzed reductive coupling of alkyl halides with terminal arylalkynes. J. Am. Chem. Soc. *137*, 4932–4935.

61. Dugave, C., and Demange, L. (2003). cis–trans isomerization of organic molecules and biomolecules: implications and applications. Chem. Rev. *103*, 2475–2532.

62. Gaspari, R., Prota, A.E., Bargsten, K., Cavalli, A., and Steinmetz, M.O. (2017). Structural Basis of *cis* - and *trans* -Combretastatin Binding to tubulin. Chem *2*, 102–113.

63. Liu, P., and Jacobsen, E.N. (2001). Total synthesis of (+)-ambruticin. J. Am. Chem. Soc. *123*, 10772–10773.

64. Zeng, J., Vedachalam, S., Xiang, S., and Liu, X.-W. (2011). Direct *C*-glycosylation of Organotrifluoroborates with glycosyl fluorides and its application to the total synthesis of (+)-Varitriol. Org. Lett. *13*, 42–45.

65. Nicolas, L., Angibaud, P., Stansfield, I., Bonnet, P., Meerpoel, L., Reymond, S., and Cossy, J. (2012). Diastereoselective metal-catalyzed synthesis of *C*-aryl and *C*-vinyl glycosides. Angew. Chem. Int. Ed. Engl. *51*, 11101–11104.

66. Liu, J., and Gong, H. (2018). Stereoselective Preparation of α- *C*-vinyl/aryl glycosides via Nickel-Catalyzed Reductive Coupling of glycosyl Halides with vinyl and aryl Halides. Org. Lett. *20*, 7991–7995.

67. Jeanneret, R.A., Johnson, S.E., and Galan, M.C. (2020). Conformationally constrained glycosyl donors as tools to control glycosylation outcomes. J. Org. Chem. *85*, 15801–15826.

68. Kessler, H., Wittmann, V., Köck, M., and Kottenhahn, M. (1992). Synthesis of *C*-glycopeptides via free radical addition of glycosyl bromides to dehydroalanine derivatives. Angew. Chem. Int. Ed. Engl. *31*, 902–904.

69. Anderson, M.B., Kobayashi, Y., Ito, K., Holme, K.R., Cui, J., Fugedi, P., Peto, C.F., Wang, L.H. (1999). Preparation of sialyl Lewis X and sialyl Lewis A glycomimetics as selectin inhibitors. U.S Patent WO 9929705, filed, December 4, 1997 and granted June 17, 1999.

70. Lu, X., Wang, X.-X., Gong, T.-J., Pi, J.-J., He, S.-J., and Fu, Y. (2019). Nickel-catalyzed allylic defluorinative alkylation of trifluoromethyl alkenes with reductive decarboxylation of redox-active esters. Chem. Sci. *10*, 809–814.

71. Huihui, K.M., Caputo, J.A., Melchor, Z., Olivares, A.M., Spiewak, A.M., Johnson, K.A., DiBenedetto, T.A., Kim, S., Ackerman, L.K., and Weix, D.J. (2016). Decarboxylative cross-electrophile coupling of *N*-Hydroxyphthalimide esters with aryl iodides. J. Am. Chem. Soc. *138*, 5016–5019.

72. Yang, J., Zhang, J., Qi, L., Hu, C., and Chen, Y. (2015). Visible-light-induced chemoselective reductive decarboxylative alkynylation under biomolecule-compatible conditions. Chem. Commun. (Camb) *51*, 5275–5278.

73. Kawamata, T., Yamaguchi, A., Nagatomo, M., and Inoue, M. (2018). Convergent total synthesis of asimicin via decarbonylative radical dimerization. Chem. Eur. J. *24*, 18907–18912.

74. Adak, L., Kawamura, S., Toma, G., Takenaka, T., Isozaki, K., Takaya, H., Orita, A., Li, H.C., Shing, T.K.M., and Nakamura, M. (2017). Synthesis of aryl *C*-glycosides via iron-catalyzed cross coupling of halosugars: stereoselective anomeric arylation of glycosyl radicals. J. Am. Chem. Soc. *139*, 10693–10701.

75. Tarantino, K.T., Miller, D.C., Callon, T.A., and Knowles, R.R. (2015). Bond-weakening catalysis: conjugate aminations enabled by the soft homolysis of strong N-H bonds. J. Am. Chem. Soc. *137*, 6440–6443.

76. Zhang, Z., Stückrath, J.B., Grimme, S., and Gansäuer, A. (2021). Titanocene-catalyzed [2+2] cycloaddition of Bisenones and comparison with photoredox catalysis and established methods. Angew. Chem. Int. Ed. Engl. *60*, 14339–14344.

77. Wan, S., Luo, Z., Xu, X., Yu, H., Li, J., Pan, Y., Zhang, X., Xu, L., and Cao, R. (2021). Manganese(I)-catalyzed site-selective C6-alkenylation of 2-pyridones using alkynes via C–H activation. Adv. Synth. Catal. *363*, 2586–2593.