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Titanium(III) Reagents in Carbohydrate Chemistry: Glycal and *C*-Glycoside Synthesis

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Abstract—Titanocene(III) chloride and zirconcene(III) chloride are effective and mild reagents for radical generation in organic synthesis. In carbohydrate chemistry, these species are useful for the conversion of glycosyl halides to glycals, and for the stereospecific preparation of *C*-glycosides. In all cases, the 1-glycosyl radical is an active intermediate, generated by reaction of carbohydrate substrates with the organometallic. © 2000 Elsevier Science Ltd. All rights reserved.

Overview of Organic Synthesis with Titanium(III) Reagents

Titanium(III) compounds, which are metal centered radicals, are a group of mild reagents with diverse applications in organic synthesis. Titanocene(III) species derived from $Cp_2Ti^{III}BH_4$ have been used to reduce both aryl and alkyl halides,[1–3] as well as ketones,[4] aldehydes,[4] and aromatic azo compounds.[5] A titanocene(III) hydride is the active reductant;[4] titanocene(III) hydrides are also proposed for the hydrosilylation of lactones, esters, and ketones.[6,7] Titanocene(III) chloride ($[Cp_2TiCl]_2$, **1**) is an effective reducing agent for a variety of compounds,[8,9] including epoxides.[10–17] It also reacts with activated halides,[8,11] such as dibromides;[8,11] reduction occurs by heteroatom abstraction, which likely generates a Cp_2Ti^{IV} species and a carbon radical. The apparent requirement for alkyl halide activation, and the broad range of functional groups **1** tolerates (alcohols;[12] amines;[12] amides;[12] ketones;[18] acids;[19] esters;[12] and aromatic halides[1,3,20,21]) suggest it to be a selective reducing agent. Furthermore, **1** is neither acidic nor basic, and it operates under mild conditions; **1** seems to be ideal, therefore, as a reagent for use with sensitive, variously functionalized substrates, such as carbohydrates.

Synthesis of Titanocene Chloride (1)

Titanocene chloride (**1**) is easily prepared by reduction of titanocene dichloride (Cp_2TiCl_2, **2**) with either Zn[22] or Al metal;[23] the alkali metals tend to over reduce the Ti(IV) to Ti(II) or Ti(0) species.[8] Likewise, the initial product of zinc reduction is a bimetallic Zn–Ti complex, which must be decomposed with diethyl ether, to give **1** but only in moderate yield.[22] An improved preparation involves reduction of **2** by Al metal.[23] Simply stirring a solution of red complex **2** with Al foil or wire for 16 h gives green **1**; the color change is a helpful indicator of the reaction's progress. The dimer is isolated in very good yield by filtration of the reaction mixture, followed by concentration of the filtrate. It is also possible to generate the reagent in situ by reducing Cp_2TiCl_2 with alkyl magnesium halides,[8] zinc,[12,13] or SmI_2.[24] Ligand substitution can also be used to prepare **1**, for example by reaction of $TiCl_3$ with thallium(I) cyclopentadienide.[25]

Mechanism of Ti(III) Reductions of Substrates

Compound **1** has been shown to be a dimer by single-crystal X-ray diffraction[26] where the two d^1 Ti atoms are bridged by chloride ligands. While the Ti centers are formally $17e^-$ species, they are coordinatively saturated in the dimer. In order for **1** to react with halides and epoxides via an inner sphere mechanism, it is necessary to have an available coordination site on the metal. Coordinating solvents such as THF readily dissociate the dimer into the reactive monomeric complex.[22] Weakly coordinating solvents, such as diethyl ether and benzene, do not effectively break the dimer, and **1** is less reactive as a reductant in these solvents. The dimer can also be broken through the use of strongly coordinating ligands or solvents, such as amines, pyridines and phosphines,[26–28] or acetonitrile. But, whereas such ligands (or solvents) completely dissociate **1** into monomeric adducts, they effectively prevent any inner sphere processes, as they do not readily dissociate from the Ti(III) center to provide a site for substrate coordination.

Titanocene(III) chloride reacts with epoxides by abstractive ring-opening to generate an organic radical; trapping of Ti(III) generated radicals by a second equivalent of Ti(III)

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produces the alkyltitanium(IV) complex.[12] Elimination of 'Ti(IV)–O–Ti(IV)' from the dimetalated species gives the olefin. The addition of a hydrogen atom source (such as 1,4-cyclohexadiene or 2-methyl-2-propanethiol) to the reaction mixture allows for the isolation of alcohols in good yield.[12] The intermediate radical is simply quenched by H atom abstraction before reaction with a second equivalent of Ti(III) can occur.

Reduction of organic halides[18] by **1** involves a similar process. Facile halogen atom abstraction by **1** produces the corresponding radical. Capture of the radical by a second equivalent of **1** gives an organotitanium(IV) complex.[18] In the context of glycosyl halide activation, this process yields a (glycosyl)titanium(IV) species. β-Elimination of $Cp_2Ti^{IV}Cl(OR)$ gives the glycal in a sequence reminiscent of classical studies involving the reaction of Cr(II) with β-substituted alkyl bromides.[29]

Coupling of Ti(III)-Generated Radicals

It is possible to use unsaturated organic species to intercept alkyl radicals generated by the reaction of **1** with organic halides[30] or epoxides.[10–12,31] This technique has been used effectively in some recent synthetic efforts.[32,33] Fischer carbene complexes are also efficient traps for the alkyl radicals generated from epoxides.[34] Trapping reactions using these carbene complexes proceed in higher yield and with better selectivity than do those using organic esters. As it is possible to oxidize the metal carbenes to esters (or lactones), these carbenes act as synthons for β-substituted esters.

Titanium(III) species such as **1** or $TiCl_3$ have also been shown to induce reductive coupling of aldehydes in pinacol coupling,[19,35–39] which proceeds by initial carbonyl oxygen coordination. For **1**, such coordination generates a stabilized ketyl complex.[19] Coupling can be achieved in both anhydrous and aqueous media, as $Cp_2Ti(III)$ species are stable in deoxygenated water.[8] Dissolution of **1** in aqueous THF gives blue $[Cp_2Ti(H_2O)]^+$, which is, however, unreactive for pinacol coupling. When excess Cl^- is added, which can displace coordinated water, pinacol coupling becomes efficient.

Applications of $Cp_2Ti(III)$ in Carbohydrate Chemistry

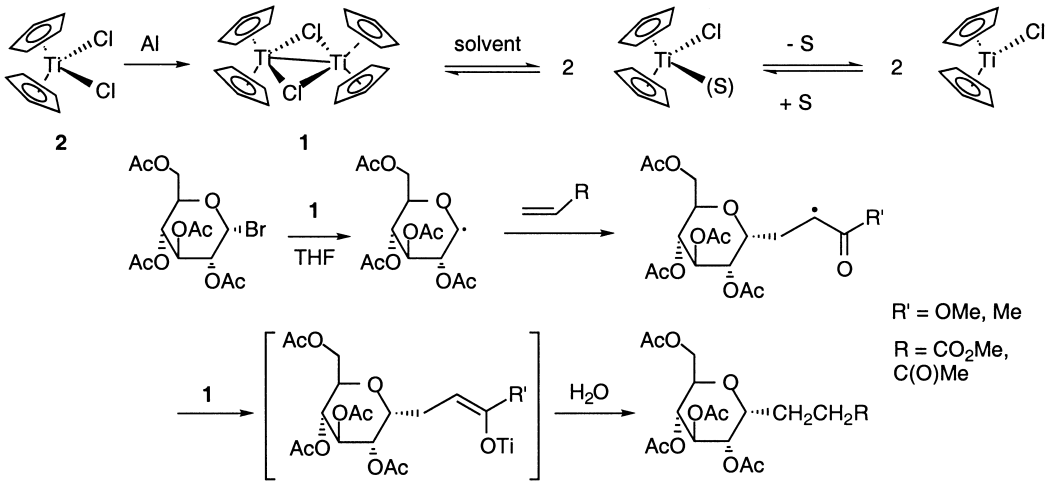
Our interest in $Cp_2Ti(III)$ reagents led us to investigate their applications in carbohydrate chemistry: it was thought that **1**, which was known to generate carbon radicals by halogen abstraction from activated halides,[18,40] could be an appropriate substitute for tin reagents for the preparation of glycosyl radicals. Unlike organotin compounds, which show high biological activity and can be readily absorbed through the skin,[41] the byproducts from Ti(III) mediated reductions are non-toxic, and can be easily recycled.[8,18,34]

In one application of Ti(III) to carbohydrate chemistry (discussed in detail below), **1** reacts with glycosyl halides to give the corresponding 1-glycosyl radicals, which are, in certain circumstances, sufficiently stable to allow for EPR analysis.[42,43] These glycosyl radicals do not decompose by disproportionation or elimination to give glycals, but they can be captured by a second equivalent of **1** gave a glycosyltitanium(IV) complex. β-Elimination of $Cp_2Ti^{IV}Cl(OR)$ from this (glycosyl)metallic gives the glycal.

Glycosyl radicals have been used as intermediates in the preparation of a variety of carbohydrate derivatives, including anhydroalditols[44] and *C*-glycosides.[45] The anomeric radical is easily generated by a variety of methods, most commonly by reaction with stannyl radicals with glycosyl halides,[46–51] selenides,[52,53] or thiocarbonyls.[54,55] Anomeric radicals have also been generated from the halides by electrochemical reduction[56] or by reaction with metal mediators.[57,58] In addition, irradiation of glycosyl–cobalt complexes induces homolytic cleavage to give the glycosyl radical.[59–61]

The coupling chemistry of a series of pento-, hexo-, and heptulo-pyranosyl radicals generated from reaction of glycosyl halides with tin hydrides (at 90°C) has been thoroughly investigated.[48] In the hexopyranose case, mannose, galactose, and glucose all yielded radicals that were trapped by olefins with high axial selectivity, forming the α-glycosidic anomers. Though no β-anomer could be observed for galactosyl and mannosyl radicals, glucosyl gave a 93:7 mixture of α- and β-glycosides.[48] When 1-glucosyl radicals are generated at low temperature, stereoselective coupling to give the α-anomer has been reported.[53,58] The effect of temperature on the stereoselectivity of tin deuteride reduction of β-glucosyl chlorides has also been noted.[62] These observations have led to the conclusion that an initially formed β-1-glycosyl radical inverts, and addition occurs via the more stable axial radical. It has been postulated that any β-isomer formed is the product of attack on the 'back' lobe of the 'axial' radical, rather than that of attack on the 'equatorial' radical; the axial 2-O substituent in mannose could thus block back side attack on the σ-radical.[45] For the galactosyl series, back side attack is less effectively blocked by the axial substituent. A similar temperature dependence was noted for the (1-alkoxy)glucosyl radical; selectivity for axial deuteride addition to the α face fell from 12:1 at 30°C to 7:1 at 110°C.[63] No interconversion of anomers has been noted under the reaction conditions.[63]

It is commonly accepted that the 1-glycosyl radical has the unpaired electron in an orbital with predominantly p character. An EPR study of variously protected 1-glucosyl radicals indicates small coupling of the unpaired spin with the β-hydrogens at C-2, and relatively large coupling to the γ-hydrogens, as compared to substrates conformationally locked in the chair conformation (for example, the 2,3;4,6-di-*O*-acetal glucopyranose-1-yl radical).[42] This has been interpreted as indicative of a conformational change in the glucosyl radical from a chair to a half-boat conformation. This interaction would provide additional stabilization for the radical by allowing overlap with the β-CO bond in a coplanar arrangement.[64] In sugars such as mannopyranose, where the β-CO bond is already in an axial position, no change in conformation is observed. The temperature effect noted on the magnitude of the observed couplings to the



Scheme 1. The synthesis of simple *C*-glycosides using **1**.

radical center in the EPR spectra indicates that the radical is conformationally flexible.

For pentopyranosyl cases, the lack of a hydroxymethyl substituent at C-5 seems to impart flexibility to the ring, too,[48,50] and mixtures of coupled products are often obtained. A comparison of the pentopyranosyl analogs in the *gluco* and *manno* series showed an apparent reversal in anomeric selectivity.[48] Xylosyl bromide (*gluco* configuration) gave only the β-anomer, whereas glucosyl bromide gave a mixture of α and β products; the lyxosyl bromide (*manno* configuration) gave a 7:3 mixture of α:β products, whereas the mannosyl bromide had given α coupling, exclusively.[48]

C-Glycoside Synthesis

Several *C*-glycosides are potent antitumor, antiviral, antibacterial or antibiotic agents.[65-67] As analogs of *O*-glycosides, these compounds have a glycosidic carbon–carbon bond; this characteristic provides stability to hydrolysis, a problem that limits the ready use of *O*-glycosides as pharmacological agents. The glycoside can be either a furanose or a pyranose, and the aglycone portion can include heterocycles (*C*-nucleosides) and aromatic systems (*C*-aryl glycosides).[68] Another class of *C*-glycosides, *C*-disaccharides, are non-metabolizable analogs of *O*-disaccharides, and are used for enzyme receptor site studies.[69–72]

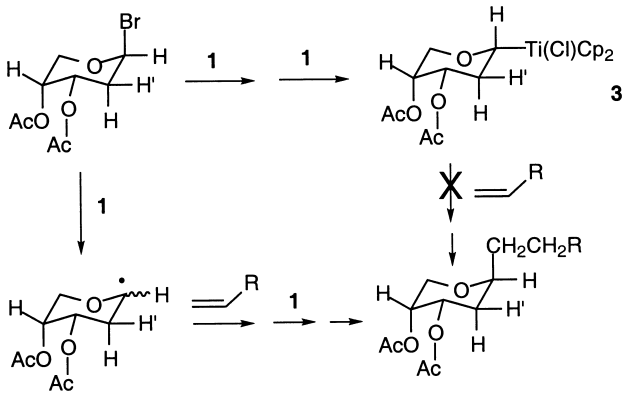
Because of their biological activity, much effort has gone into the development of synthesis methodology for *C*-glycosides.[73–77] Early attempts mirrored *O*-glycoside synthesis. For example, anomeric esters can undergo Lewis acid glycosylation to give *C*-glycosides.[78] Additionally, in situ rearrangements of *O*-glycosides to *C*-glycosides has shown some utility as a synthetic method, though with limited stereochemical control.[67,79–81] Many syntheses of *C*-glycosides take advantage of the normal electrophilic characteristics of carbohydrates, via nucleophilic attack at the anomeric center of lactones,[82–84] glycosyl halides,[68,85] or lactols.[86–88] Metallation of the anomeric center converts it to a nucleophile, in an 'umpolung' approach. Both lithiated and stannylated glycosides[89–96] and glycals [89–101] have been coupled with electrophiles such as carbonyls and ketyls. Transition metal glycosides (Co;[102,103] Mn;[104–106] Fe[107,108]) have shown only limited utility for C–C bond formation, but a recent report suggests that (2-deoxyribopyranosyl)-titanium compounds can undergo facile coupling with aldehydes to produce simple *C*-glycosides.[109,110]

An alternate approach to the synthesis of *C*-glycosides involves the reaction of 1-glycosyl radicals with unsaturated species to form C–C bonds. While Michael acceptor olefins such as acrylonitrile, methyl acrylate and methyl vinyl ketone are commonly used as radical traps, allylic species[55,111–114] and oximes[115] have also been used successfully. These produce simple *C*-glycosides with predominantly α-stereochemistry in the hexopyranosyl series. Efforts have been made to extend the radical coupling methodology to provide more elaborate *C*-glycosides. For example, the preparation of showdomycin by the utilization of a radical addition step to prepare the *C*-glycoside skeleton has been achieved.[54,116,117]

To improve the stereoselectivity of additions to anomeric radicals and to provide access into both α and β species, a variety of temporary tethers[118–120] have been used to connect the coupling species to the sugar moiety. By selecting either an α- or β-hydroxyl group, both glycosidic anomers are attainable in an intramolecular process. Consecutive radical additions to glucals extend the utility of this method. Here, reaction initiated by stannyl radicals gives addition to the double bond, and the resultant 1-glycosyl radical can then be trapped by an appropriate unsaturated species.[46,47]

Ti(III) Promoted *C*-Glycoside Synthesis

Since reaction of **1** with glycosyl halides generates the 1-glycosyl radical at room temperature, it was possible that coupling could show high stereoselectivity. Indeed, reduction of glucosyl and galactosyl bromides using **1** in



Scheme 2. Formation of the *C*-glycoside apparently does not involve a Ti(IV) organometallic.

the presence of Michael acceptors did give simple α-*C*-glycosides stereoselectively, in isolated yields comparable to other methods involving similar radical processes.[30] No β-glycoside was isolated or could be observed in the NMR spectrum of the crude reaction mixture. (The only byproduct observed in all cases was the corresponding glycal, obtained by trapping the radical with **1** followed by β-elimination.) At least two reaction pathways for C–C bond formation can be envisaged: the reaction proceeds via radical addition to the olefin (Scheme 1, as seen for tin species); or the intermediate radical reacts to form the glycosyltitanium(IV) complex in situ, which undergoes competitive conjugate addition to the olefin or fragmentation to the glycal (Scheme 2).

An authentic (glycosyl)titanium complex was prepared and examined to determine if it would undergo conjugate addition with a simple Michael acceptor. Bis(cyclopentadienyl)(3,4-di-*O*-acetyl-2-deoxy-α-D-*erythro*-pentopyranosyl)-titanium(IV) chloride (**3**) was prepared and isolated (2-*O*-substituted analogs undergo rapid β-elimination to give glycal[109,121,122]). Stirring a mixture of this ribosyltitanium complex and acrylonitrile gave only the corresponding anhydroalditol[123] upon hydrolysis; no product of conjugate addition was observed using the preformed organometallic. In contrast, reaction of 3,4-di-*O*-acetyl-2-deoxy-β-D-ribopyranosyl bromide with **1** in the presence of acrylonitrile gave a mixture of products, from which the desired β-*C*-glycoside was obtained (it was not possible to unequivocally rule out the formation of the α-glycoside here). The β-stereoselectivity observed for olefin trapping by the ribosyl radical is opposite to that found for coupling (α) in the hexopyranosyl case; however, it is in agreement with literature observations made for pentopyranosyl substrates. Interestingly, when the 2-deoxyribosyl radical is trapped by Ti(III) to generate the 2-(deoxyribosyl)titanium complex, both α- and β-anomers are produced (3:1), and the α-anomer (the equatorial product) is formed exclusively when a high concentration of **1** is maintained. If the β-anomer is the kinetic product, as adjudged based on results of irreversible trapping by an olefin, the α-isomer would be the thermodynamically preferred one. (Irreversible trapping of 1-glycosyl radicals by Sm(II) gives the kinetic organosamarium(III) product.[124]) If Ti(III) were a good leaving group under high Ti(III) concentrations, geometric equilibration of the organometallic might be possible. A similar equilibration has been observed for (glycosyl)cobaloximes; mechanistic studies[59] indicate that the α-cobaloximes undergo isomerization, via the anomeric radicals, to give the β-anomers.

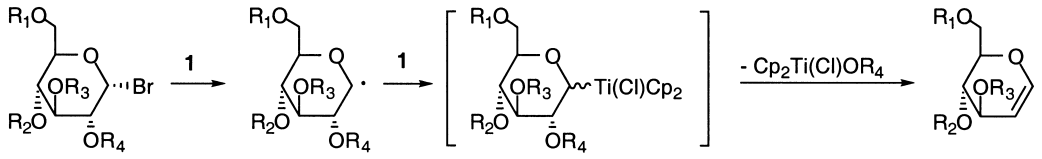
Other Considerations in Radical-Based Coupling Procedures

Radical coupling reactions performed using tin hydride derived initiation can be complicated by unwanted, further reduction: Hydrogen atom abstraction from tin hydride can terminate a radical chain process at several points as indicated by the anhydroalditol byproduct formation. When **1** is used in place of tin hydride, it seems that the initial product of radical addition to the Michael acceptor is a titanium enolate.[12,18] Substantial deuterium incorporation at C-2 was noted when an aliquot of the reaction mixture (acetobromoglucose and methyl acrylate) was quenched under N_2 with D_2O. Deuterium incorporation was approximately 80%, based on integration for the C-2 proton signal (δ2.41). These protons do not exchange with D_2O, as demonstrated using an authentic sample of the methyl acrylate adduct. The adduct radical is also not quenched by hydrogen atom abstraction from solvent: when a coupling procedure was carried out in THF-d_8, no deuterium incorporation was detected by NMR. Elaboration[125–128] of this enolate intermediate may be possible.

Synthesis of Glycals

The classical preparation of glycals was reported in 1913 by Fischer and Zach,[44] and these carbohydrate derivatives have since proven to be versatile chiral intermediates for organic synthesis.[129,130] The double bond allows the preparation of a variety of monosaccharide derivatives through hydration,[131] hydrogenation,[131] epoxidation,[132–136] or allylation.[137] Glycals have been starting materials in complex synthesis, including that of brevitoxin,[138] tetrahydropyranoid antibiotics,[139] *C*-glycosides,[75,140–144] and okadaic acid.[145] An elegant 'glycal assembly strategy' for the formation of oligosaccharides, via reaction of 1,2-anhydro sugars (glycosyl donors) with glycals (glycosyl acceptors) has been described in detail.[146–148] Following coupling, epoxidation of the glycal converts it to a glycosyl acceptor and allows reaction with a second glycal equivalent to continue the sequence. Despite their well-documented uses as intermediates, however, straightforward and mild routes for preparing differentially substituted glycals had remained limited, until recently.

Glycals are often prepared by the reduction of peracetylated glycosyl bromides with zinc in acetic acid;[149,150] this method gives pyranoid glycals in good yield, but it is unsuitable for the reduction of furanosyl halides, since rapid elimination occurs to give the furan under these acidic conditions. It has been suggested that heterolytic cleavage of the C–Br bond occurs under these acidic conditions to give a carbocation, which is then reduced by electron transfer from zinc, although no conclusive evidence has been presented in support of the mechanism.[151] Indeed, while no glycosyl



Scheme 3. Glycal synthesis using **1**.

zinc compounds have been isolated, it is possible that a transient organometallic is formed.[44]

The vigorous conditions of the Fischer–Zach synthesis are limited to acetylpyranosyl halides; many modern synthetic routes to glycals also involve glycosyl halide reduction and can give the glycal under non-acidic conditions. Reducing agents used with protected glycosyl halides include sodium and potassium metal,[152] sodium naphthalide,[152] zinc/silver graphite,[153] aluminum amalgam,[154] SmI_2,[124,155] potassium graphite,[156] lithium/ammonia,[157,158] chromium(II),[159,160] zinc/base,[161] and Co(II).[162] Reductive fragmentation of an *O*-alkylidene group,[152,163] or reductive elimination from C-2 sulfonates at C-2 have also been reported.[164-166] Electrochemical reduction of glycosyl halides by mercury electrodes gives the glycal, in moderate yield.[167] In some cases, such as in reduction by Sm(II)[124,155] or Cr(II),[159] organometallic compounds have been identified as intermediates; even if unisolated, they might prove to be of use for C–C bond formation in the context of *C*-glycoside synthesis. However, many of these methods suffer from limited protecting group compatibility,[159] and although Sm(II) is a relatively mild and selective reagent, its cost is prohibitive for use on a large scale.

Although glycosyl halides are readily available, hydrolysis or other decomposition routes can be problematic, especially for bromides. Thus, glycosyl derivatives otherwise substituted at C-1 have been used as glycal precursors by reduction. Thiophenyl glycosides and glycosyl phenylsulfones give the glycal when treated with lithium naphthalide[168] or SmI_2.[124,155] In the latter case, electron transfer to the glycosyl phenylsulfone is proposed to generate the 1-glycosyl radical; the (glycosyl)samarium compound is then formed,[124,155] and β-acetate elimination gives the glycal. Glycals are also prepared by treatment of 1-glycosyl sulfoxides with organolithium reagents.[169] Here, reaction is thought to occur by formation of the C-1 carbanion followed by β-elimination. Reaction of 2,3-anhydro sugars with either methyllithium (formed in situ from methyl iodide and lithium metal)[170] or ethylmagnesium bromide/copper iodide[171] gives the corresponding glycal; the 2-deoxy-2-iodo sugar is the reactive intermediate.[172] Deoxygenation of either 1,2-anhydro sugars by dialkylphosphoselenic acids[173] or of 1,2-thiocarbonates by tributyltin hydride have also been used to produce glycals.

Clearly, there exists a wide range of glycal synthesis methodology. However, improvements are still in order: protecting group use is limited, either by acidic or basic reaction conditions,[149,153,159] or by competitive reduction of other functionality.[157,158,168] Furthermore, some methodologies involve reagents that are pyrophoric[153,156] or toxic,[154,159] or require specialized substrates.[170–172]

Ti(III) Mediated Glycal Synthesis: the Effect of the C-1 Substituent

Since **1** readily dehalogenates activated alkyl halides[18] by simple and selective halogen atom abstraction, this reagent seemed interesting to consider for selective transformations of glycosyl halides. Indeed, it was found that treatment of peracetylated glycosyl bromides with **1** gave the corresponding glycals rapidly and in high yield.[109,121,122] It is interesting that elimination occurs regardless of the stereochemistry at C-2; both glycosyl and mannosyl bromide give glucal in excellent yield (Scheme 3).

A radical-based mechanism is reasonable to account for glycal formation in the reaction between **1** and the glycosyl halide: initial halide abstraction gives the 1-glycosyl radical; this radical is trapped by a second equivalent of Ti(III), which gives the (glycosyl)titanium(IV) species; β-elimination of $Cp_2TiCl(OAc)$ gives the glycal. A variety of pyranoid glycals have been prepared by this route.[121,122] Furanoid glycals are difficult to isolate under these conditions, as is usual for most methods for formation of glycals: when the substituent at C-3 is a good leaving group, elimination to form the furan is rapid.[174] β-Elimination apparently occurs from (glycosyl)Ti(IV) complexes having either a relative *cis* or *trans* configuration at C-1 and C-2; it appears that elimination could occur via either a *syn*-(coordinative) or *anti*-elimination pathway, assuming that the α-glycosyl titanium intermediate is formed in both mannosyl and glucosyl cases: based on published reports[46,48,49,53,54,58,62,175] the α-radical is preferred in hexopyranosyl cases, and axial trapping of this radical by Ti(III) is expected to be the favored path. Reduction of variously protected glycosyl halides by **1** is highly specific for halide atom abstraction; no reaction was observed with hydroxyl, acetyl, or methoxy substitution at the anomeric center. The observed reactivity of glycosyl halide mirrors C–X bond strength: 1-fluoroglycosides are unreactive, and chlorides are less reactive than the corresponding bromides. Indeed, it is possible to selectively reduce mannosyl bromide in the presence of the chloride analog.[122]

Analysis of the reaction between **1** and 3,4-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentopyranosyl bromide provides support for a mechanism involving an organotitanium(IV) intermediate. Since this sugar lacks heteroatomic substitution at C-2, β-elimination would not be favored (apparently, β-hydride elimination in $Cp_2Ti(IV)$ alkyls is slow). A solution of the ribosyl bromide was slowly added to a solution of **1** in benzene over a period of 2 h. Following the color change from green to red, Cp_2(3,4-di-*O*-acetyl-2-deoxy-D-*erythro*-pentopyranosyl)TiCl (**3**) was isolated as an orange–red crystalline solid. ^1H NMR analysis of the product obtained using a stoichiometric amount of **1** showed it to

be a 3:1 mixture of α- and β-anomers; if the bromide is added to a small excess of **1**, α-anomer **3a** could be obtained exclusively.[109]

The isolation of glycosyl derivatives of several transition metals other than Ti, has also been accomplished. Glycosyl metallic compounds formed by nucleophilic attack on the anomeric carbon give rise to mixtures of products and exhibit varying stereoselectivity in the mannosyl and glucosyl cases. For instance, the α-(glucosyl)manganese pentacarbonyl complex is formed by reaction of the halide with sodium (pentacarbonyl)manganate, but the mannosyl halide gives a 1:2 mixture of α and β products.[104,105] Similarly, glycosylcobaloximes prepared from glycosyl halides and $NaCo(dmgH)_2py$ in acetonitrile give products of mixed stereochemistries from mannosyl and glucosyl substrates,[61] but glycosylcobaloximes formed from the glycosyl radicals in aqueous solutions exhibit a preference for α-products.[59]

Effect of the C-2 Substituent

Details of the mechanism of elimination for the C-2-*O* substituent are largely unknown for (glycosyl)titanium, but this process seems fast and general. Facile elimination occurs for C-1 lithiated glycosides with a variety of C-2-*O* protecting groups,[176] including 2-*O*-benzyl, 2-*O*-acetyl, and 2-*O*-methoxy. Glycal formation was noted for these substituents, and also for 2-OH, using **1**. Elimination does not occur rapidly for 2-*O*-silylated mannosyl- and glucosyl-Sm(III) compounds,[177] but glycal was prepared readily from the reaction of **1** and the 2-*O*TMS glycosyl chloride. Treating a 2,3-cyclic acetal derivative with **1** gives the free allylic alcohol-substituted glycal by acetal ring fragmentation.[152,153,156–158] Reaction of 2,3:4,6-di-*O*-isopropylidenemannopyranosyl bromide with **1** gave 4,6-*O*-isopropylidene glucal.[178] An acetal fragmentation step was also observed in the furanosyl case. Commercially available 2,3;5,6-di-*O*-isopropylidene-mannosylfuranose was converted to the furanosyl bromide **6**, which was then treated with **1**; however, the expected furanoid glycal[152,158] rapidly decomposed to give furan[152] during attempted purification.

Functional Group Compatibility

Preparation of selectively protected glycals for further elaboration can be problematic. It is difficult to achieve simultaneous protection of C-4 and C-6 -OH, yet leave an allylic -OH unprotected. Although silylation of glycals can be achieved under mild conditions,[179–182] the use of ethers or, especially, acetal protecting groups can be compromised by the forcing synthesis conditions required for -OH group activation. In some cases, ether synthesis requires undesirable organotin intermediates.[183] Low selectivity for acetalization can also be problematic; indeed, actetalization under normal conditions gives rise to a mixture of products, from which the 4,6-*O*-acetal–glycal can be isolated in low yield.[178,184] Benzoate ester or benzyl ether introduction can be compromised by rearrangement, or by incomplete reaction.[179,180,184] Novel methods have been introduced to enable formation of protected glycals under mild conditions (e.g. enzymatic introduction of acetyl and benzoyl esters;[185] electrochemical formation of benzyl and methyl ethers;[186] and phase transfer catalysis to prepare benzyl ethers[187]), yet few general methods enable the rapid preparation of variously and specifically hydroxyl group-protected glycals. In contrast, reaction of variously protected glycosyl halides with **1** is straightforward and high yielding. All common carbohydrate protecting groups, including silyl ethers, acetals, benzyl ethers, and benzoyl esters, were found compatible with glycal synthesis conditions. Ti(III) species **1** seems, therefore, to be a reagent of general use to prepare glycals variously and selectively protected by either acid- and base-labile moieties (or both).[109,122]

The Use of Zr(III) for Glycal Synthesis

The Zr(III) analog of **1**, $(Cp_2ZrCl)_2$ (**4**)[188] has been shown to be effective for the reduction of alkyl halides, and its use was investigated for glycal synthesis. Reaction of 6-*O*-benzoyl-2,3,4-tri-*O*-acetyl-glucosyl bromide with 2 equivalents of **4** gave only 60% conversion to glucal after 30 min. In comparison, Ti(III) effects complete reduction after only 15 min. For reduction to proceed, a vacant coordination site is needed on the metal center. For Ti(III), the dimer is easily broken by the use of coordinating solvents to enable coordination of the halide; however, Zr(III) forms a much stronger dimer. Crystallographic data suggest that there is a strong Zr–Zr bond[189] in **4** which might preclude ready dissociation into the reactive monomer. As was noted for Ti(III), there was no observed reaction of **4** with peracetylated glucose.

Summary

Radical reactions exhibit higher selectivity and functional group tolerance than most ionic processes, and have demonstrated great utility in carbohydrate chemistry. Titanium(III) reagents are inexpensive and non-toxic alternatives for samarium(II) and tin(IV) reagents. As interest in glycals and *C*-glycosides grows, it is necessary to have simple, efficient methods for their preparation available. Complexes such as **1**, which tolerate a wide range of functionality, are appropriate for use with complex polyhydroxylated substrates such as sugars, and should prove to be important tools in organic chemistry.

Experimental

Organometallic reactions were performed under a blanket of N_2 in a Vacuum Atmospheres dry box. Carbohydrate substrates and other materials were obtained from Sigma or Aldrich and were used without further purification, unless otherwise noted. Methyl vinyl ketone, acrylonitrile and methyl acrylate were evaporatively distilled before use and stored under N_2 at −40°C. Solvents were obtained from EM Science and distilled under N_2 according to standard methods (THF and diethyl ether from sodium benzophenone ketyl, methylene chloride from CaH_2, and benzene from sodium metal). Flash chromatography using Aldrich silica gel (200–430 mesh) was used for product separations. Analytical thin layer chromatography was

performed on Selecto Scientific TLC Plates (200 μm) using UV light or staining (anisaldehyde, permanganate, or sulfuric acid stains) for visualization. Preparative TLC was performed on Analtech Tapered GF Uniplate Plates or Analtech Silica Gel GF Preparative Uniplates (2000 μm).

Dicyclopentadienyltitanium(III) chloride (1).[23] A solution of 4.0 g of titanocene dichloride (16.1 mmol) was stirred with 2.0 g of aluminum foil (74.1 mmol) in 25 mL of THF under N_2 overnight. The green solution was filtered and the filtrate was concentrated to dryness. The green powder was washed with diethyl ether (3×25 mL) and dried in vacuo to give a quantitative yield of **1**.

General method for the reductive preparation of glycals from glycosyl halides.[121] Glycals were prepared according to a standard procedure, for which a representative example is given for tri-*O*-acetyl–glucal (**5a**). A solution of **1** (300 mg, 0.702 mmol) in 10 mL of THF was prepared under N_2. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (200 mg, 0.486 mmol) in 10 mL of THF was added by drops to this green solution. The reaction mixture turned brown, and within 10 min was red. The mixture was concentrated, dissolved, and passed through a short column of silica to remove metallic impurities; the clear solution obtained was concentrated and dried in vacuo to give 108 mg of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol[159] as an oil (82%).

General method for Ti(III) mediated *C*-glycoside synthesis.[30] In a typical procedure, 50 mg of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.12 mmol) and 200 mg of methyl acrylate (2.40 mmol, 20 equiv.) were dissolved in 2 mL of THF under N_2 at room temperature. A green solution of 130 mg of **1** in 25 mL of THF (0.30 mmol, 2.5 equiv. of dimer) was added by drops at room temperature over 30 min. The red reaction mixture was quenched by pouring into 15 mL of water. Extraction, drying, and flash chromatography (Et_2O) gave the *C*-glycoside. All yields were calculated from ^1H NMR spectra.

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