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Mini Review

Metal glycosylidenes: novel organometallic tools for *C*-glycosidation☆ Part 19. Organotransition metal modified sugars

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Abstract

Different synthetic methodologies have been developed for the introduction of the 'Fischer-type carbene functionality' into a carbohydrate skeleton. The $K_2M(CO)_5$-'dianion' approach (M = Cr, Mo, W) provides access to metal iminoglycosylidenes. Stoichiometric metathesis with highly electrophilic pentacarbonyl[(diphenyl)carbene]chromium is applied to the synthesis of furanosylidene complexes; chromium pyranosylidenes are accessible by addition of lithioglucals to the donor-stabilized pentacarbonylchromium fragment. Sugar-derived propynols have been applied to the synthesis of vinylcarbene complexes, which undergo stereoselective *C*-glycosidation and C–C-bond formation in the carbohydrate backbone. An aminolysis/Mitsunobu recyclisation sequence provides a straightforward route to C-4 stereoinverted metal iminofuranosylidenes. Vinylchromate intermediates allow for stereoselective labeling and alkylation at C-2. Insertion of electron-rich alkynes into the metal–carbene carbon bond leads to novel organometallic *C*-glycosides. Carbohydrate-derived vinylcarbene complexes undergo diastereoselective Diels–Alder and Michael reactions. In addition to these ligand-centered reactions the chromiumcarbonyl fragment may serve as a template for [3 + 2 + 1] benzannulation, cyclopropanation and photocarbonylation. This methodology has been applied to the metal-mediated stereoselective synthesis of densely functionalized chromans, novel anomeric spirocyclopropanes and *C*-disaccharides.

Keywords: Carbene complexes; Carbohydrates; Glycosylidenes; *C*-Glycosidation; Asymmetric synthesis

1. Introduction

Carbohydrates play a prominent role in numerous biological processes such as tumor-cell growth [2], bacterial and viral infection or inhibition of glycosidases [3]. Intense research has been devoted to the development of synthetic methods for the preparation of *C*-glycosides during the past decade [4]. These efforts have been stimulated by naturally occurring *C*-nucleosides [5] and macrolides [6] with antibiotic and cytotoxic properties as well as by the prospect of glycosidase-resistant carbohydrate mimetics [7]. A variety of synthetic methodology has been developed for *C*-glycosidation; however, keeping in mind both the multifunctionality of carbohydrates and how the extent organometallic chemistry has contributed to the recent progress of stereoselective synthesis, it is surprising that organotransition metal-based reagents had only a marginal impact on this field of research so far. Their application towards the activation of the anomeric center for carbon–carbon bond formation is mainly restricted to samarium and palladium [8]. Glycosyl carbonyl complexes of iron and manganese have been synthesized [9],

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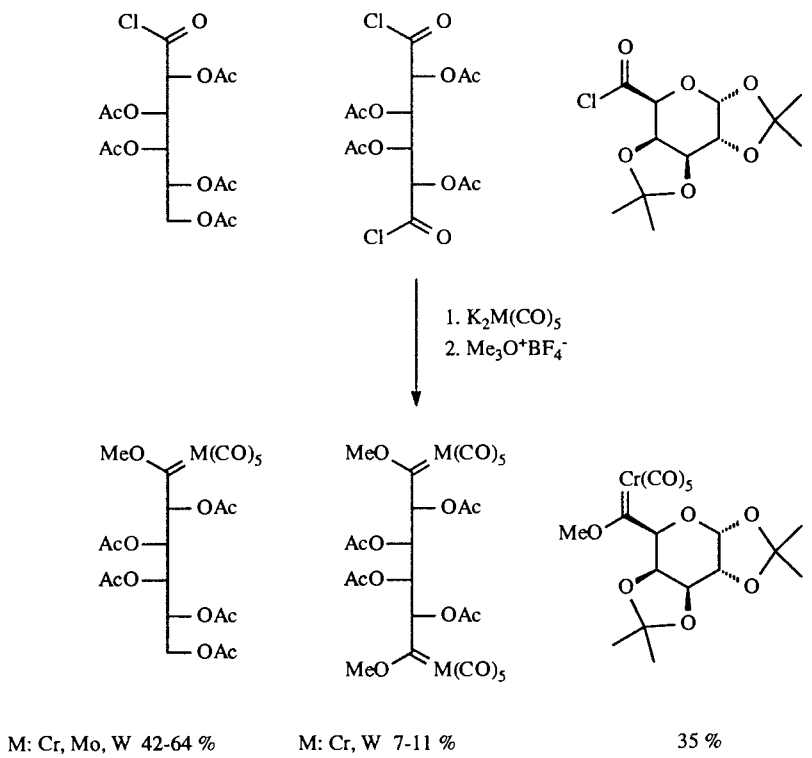
and the manganese complexes permit efficient insertion of carbon monoxide, alkenes and alkynes. However, a broader application of these compounds in *C*-glycosidation has been hampered by high pressure conditions required for the insertion of C–C multiple bond systems [10]. Encouraged by the synthetic potential of Fischer-type carbene complexes [11] as demonstrated by chemo-, regio- and often stereoselective ligand- or metal-centered reactions carried out under thermal, photochemical or sonochemical conditions [12], we became interested in organotransition metal carbohydrate derivatives bearing a Fischer-type metal carbene label in the anomeric position.

The first examples of metal carbene modified sugars have been obtained by addition of carbohydrates to isonitrile complexes of gold and platinum leading to stable glycosylamino carbene complexes [13,14]. Carbohydrates attached to the carbene carbon via an oxygen bridge have been applied as chiral auxiliaries in diastereoselective ligand substitution reactions of cationic manganese and rhenium carbyne complexes [15]. Group 6 transition metal glycosyloxycarbene complexes have been synthesized by Michael-type addition of carbohydrates to α,β-unsaturated carbene complexes [16], or by transesterification of acyloxycarbene manganese and chromium intermediates 15c. Previous work from our group focussing on synthetic, structural and conformational aspects in this area has been reviewed [17]. In this report, we will summarize recent developments in synthesis and applications of transition metal glycosylidenes, which represent metal-stabilized analogues of 'glycosylidene carbenes' [18] in which the former anomeric carbon atom is modified into a Fischer-type carbene center.

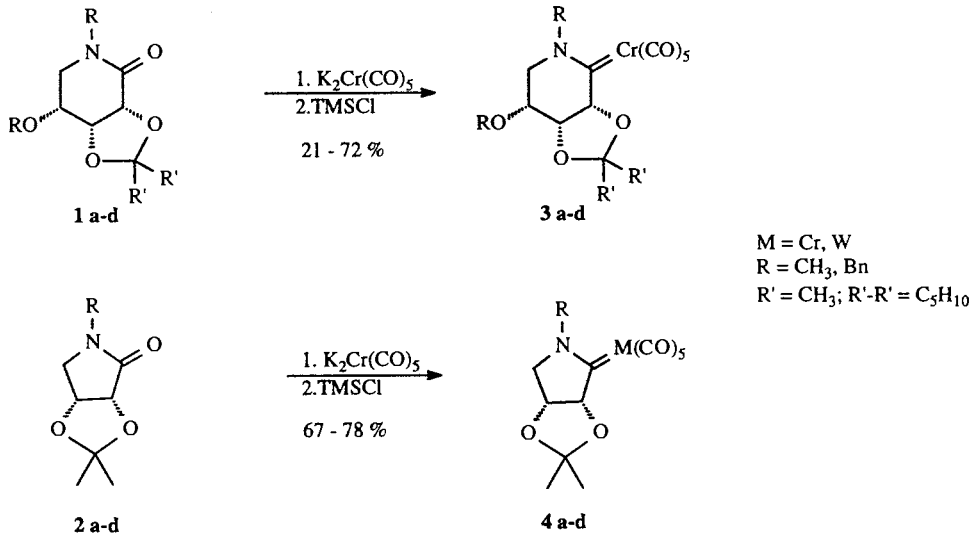
2. Synthesis of glycosylidene complexes

We have developed complementary routes to Group 6 transition metal glycosylidene complexes. The first syntheses were based on the addition of pentacarbonylmetallate dianions [19] to acyclic aldonic acid chlorides [20] and galactaric acid chlorides [21] as well as to galacturonic acid chlorides [22] followed by alkylation of the acyl metalate intermediates by trialkyloxonium salts (Scheme 1).

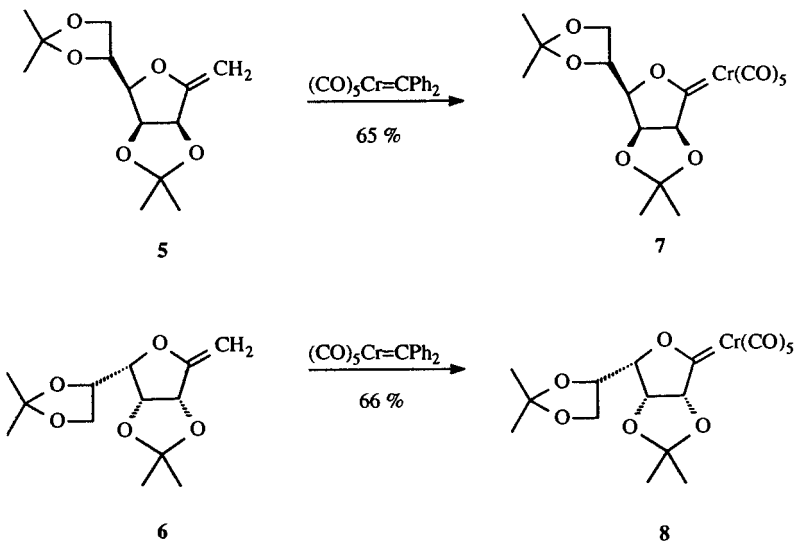
In nature, carbohydrates predominantly occur in cyclic pyranose or furanose forms which makes methods for the preparation of cyclic glycosylidene complexes highly desirable. A modification of the metalate dianion approach has been applied to the synthesis of metal iminoglycosylidenes. These complexes represent potential organometallic precursors in the synthesis of imino-*C*-glycosides [23] which are considered as transition state analogues in enzymatic glycosidation reactions [24], and thus have received considerable attention as iminosugar glycosidase inhibitors. Glyconolactams such as pyranonolactams **1** or furanonolactams **2** can



Scheme 1. Modification of sugar acid chlorides into mono and bis metal carbenes.



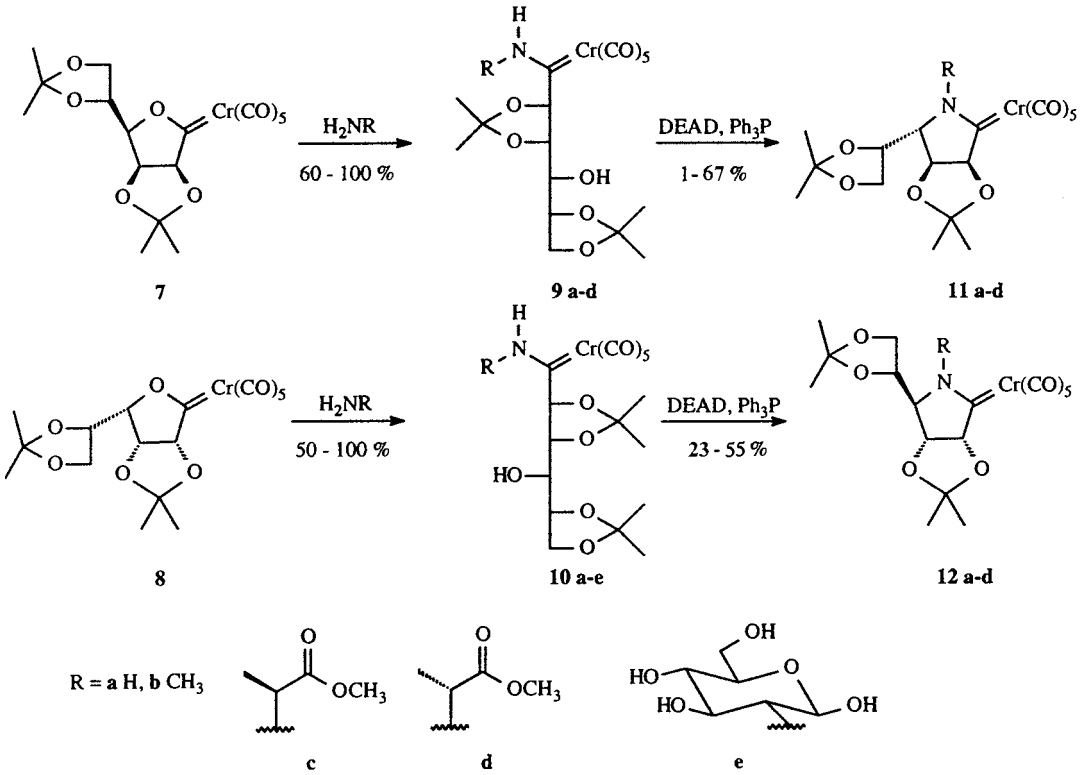
Scheme 2. Synthesis of iminofuranosylidene and iminopyranosylidene complexes via the dianion route.



Scheme 3. Cyclic glycosylidene complexes via stoichiometric olefin metathesis.

be efficiently transformed into the corresponding iminoglycosylidene complexes **3** or **4** by addition of potassium pentacarbonylmetallates followed by deoxygenation with trimethylsilyl chloride (Scheme 2) [25]. The success of this approach depends on the nature of the protective groups. Best results were obtained with 1,2-di-*O*-isopropylidene protected lactams whereas benzyl groups tend to favour elimination under the reaction conditions leading to α,β-unsaturated lactams. While these approaches make use of somewhat tedious metallate reagents, they provide access to a broad range of acyclic and cyclic sugar carbene complexes of Group 6 metals.

Attempts to apply the strongly basic pentacarbonylmetalate dianions to the synthesis of sugar-derived lactones resulted in ring-opening rather than in metal carbene functionalization 19b. We therefore devised another approach using stoichiometric olefin metathesis 12o of *exo*-glycals with highly electrophilic Fischer-type diphenylcarbene complexes (Scheme 3) 25a[26]. The thermodynamic driving force of the reaction is the formation of the better stabilized, less electrophilic Fischer-type carbene complex. While not efficient in the tungsten series, this procedure proved particularly advantageous for the preparation of chromium furanosylidene complexes such as **7** and **8** that were obtained in high yield and in multigram quantities. Chromium pyranosylidenes, although spectroscopically detectable, could not be isolated probably due to destabilizing steric interactions of the C-2-substituent with the bulky pentacarbonyl chromium fragment.

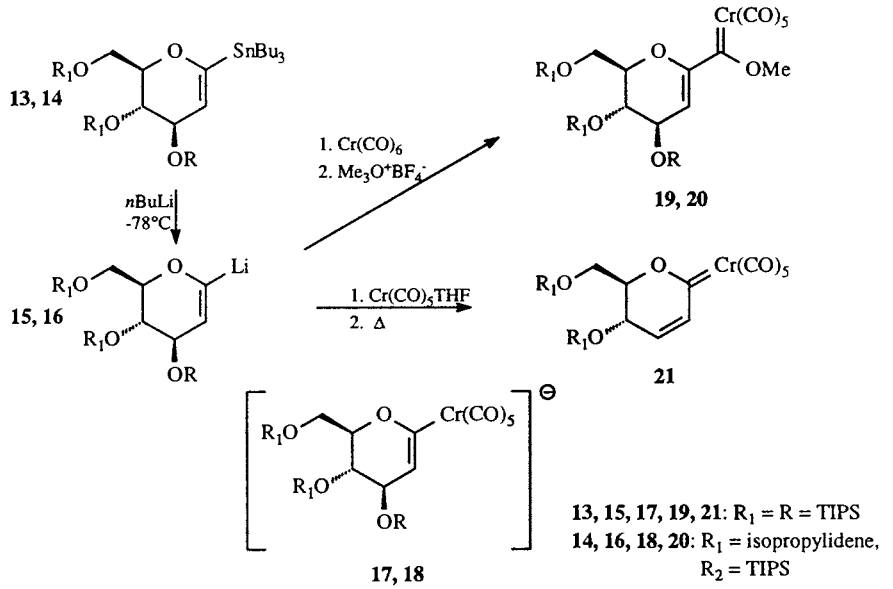


Scheme 4. 1,4-Iminoglycosylidene complexes via ring-opening aminolysis/Mitsunobu-recyclization with inversion of configuration.

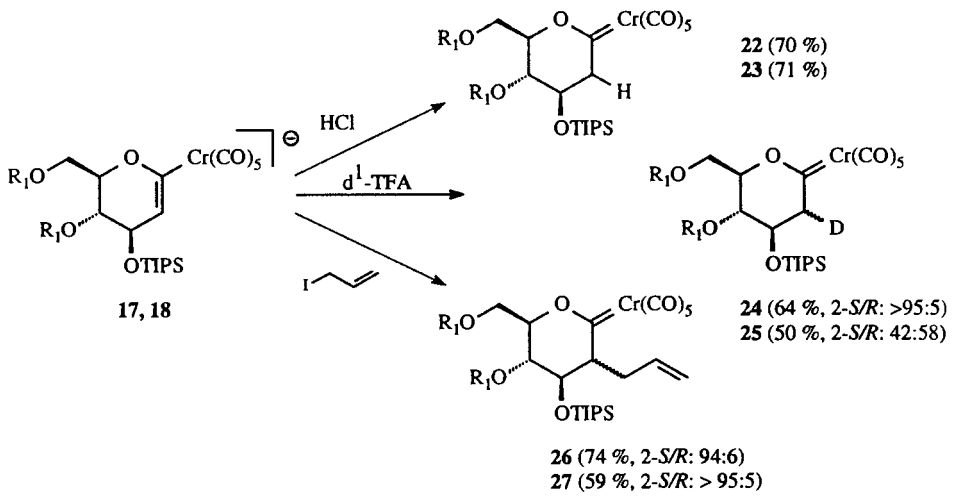
Aminolysis 12a[27] of alkoxycarbene complexes is a smooth and high-yielding reaction that has been also applied to the modification of glycosylidene complexes [17]. A variety of amines converted furanosylidene complexes **7** and **8** *E*-selectively into the corresponding acyclic aminoglycosylidene complexes **9** and **10** under mild conditions in good to excellent yields (Scheme 4). Compounds such as **9c**, **d** and **10c**, **d**, organometallic analogues of glycosyl amino acid esters, which have been evaluated as potential sialidase inhibitors [27], are readily accessible in a straightforward aminolysis of glycosylidene complexes by amino acid esters. The manno-configurated complex **7** required significantly higher temperatures than **8** for the reaction with alanine esters, which might result from steric congestion caused by different relative configurations at C-5. Aminolysis with glucosamine resulted in a 50% yield of *N*-disaccharide (**10e**), a rare example of a neutral water-soluble carbene complex.

These acyclic aminocarbene complexes bear a selectively unprotected hydroxy group at C-4 which allows recyclization reactions to give 1,4-iminoglycosylidene complexes. The reduced nucleophilicity of the aminocarbene nitrogen atom can be overcome by transforming the hydroxy substituent at C-4 into a good leaving group under Mitsunobu conditions. Thus, a complementary straightforward route to metal-modified iminofuranoses was established while the syntheses of their lactam counterparts are often lengthy and tedious. Unless bulky amines like amino acids are used, the ring-opening aminolysis/Mitsunobu-recyclization to iminofuranosylidene complexes can be performed as a one-pot procedure; it occurs with the inversion of configuration at C-4 providing access to less common sugar skeletons [28].

Glycals are versatile precursors in carbohydrate chemistry [29]. The reaction of 1-lithioglucals [30] **15** and **16**, prepared via transmetalation of the corresponding 1-stannylated glucals **13** and **14**, with Group 6 metal carbonyls is controlled by the substitution pattern of the carbonyl complexes [31]. According to the classical Fischer-route for the synthesis of carbene complexes [11], the addition of the lithiated glycal to hexacarbonyl chromium occurs at the carbonyl carbon yielding α, β-unsaturated carbene complexes **19**, **20** after methylation of the acylchromate intermediate [32]. Similar glycal carbene complexes have been obtained by direct lithiation of glycals bearing an anion-stabilizing chlorine substituent in the C-2-position (vide infra) [33]. However, if a single carbonyl ligand is replaced by a ligand combining good leaving group and good donor properties such as triphenylphosphine or tetrahydrofuran, the lithioglucal rather adds at the metal to generate vinyl chromates **17**, **18** which correspond to enolate-type pentacarbonyl chromium intermediates (Scheme 5) [34].



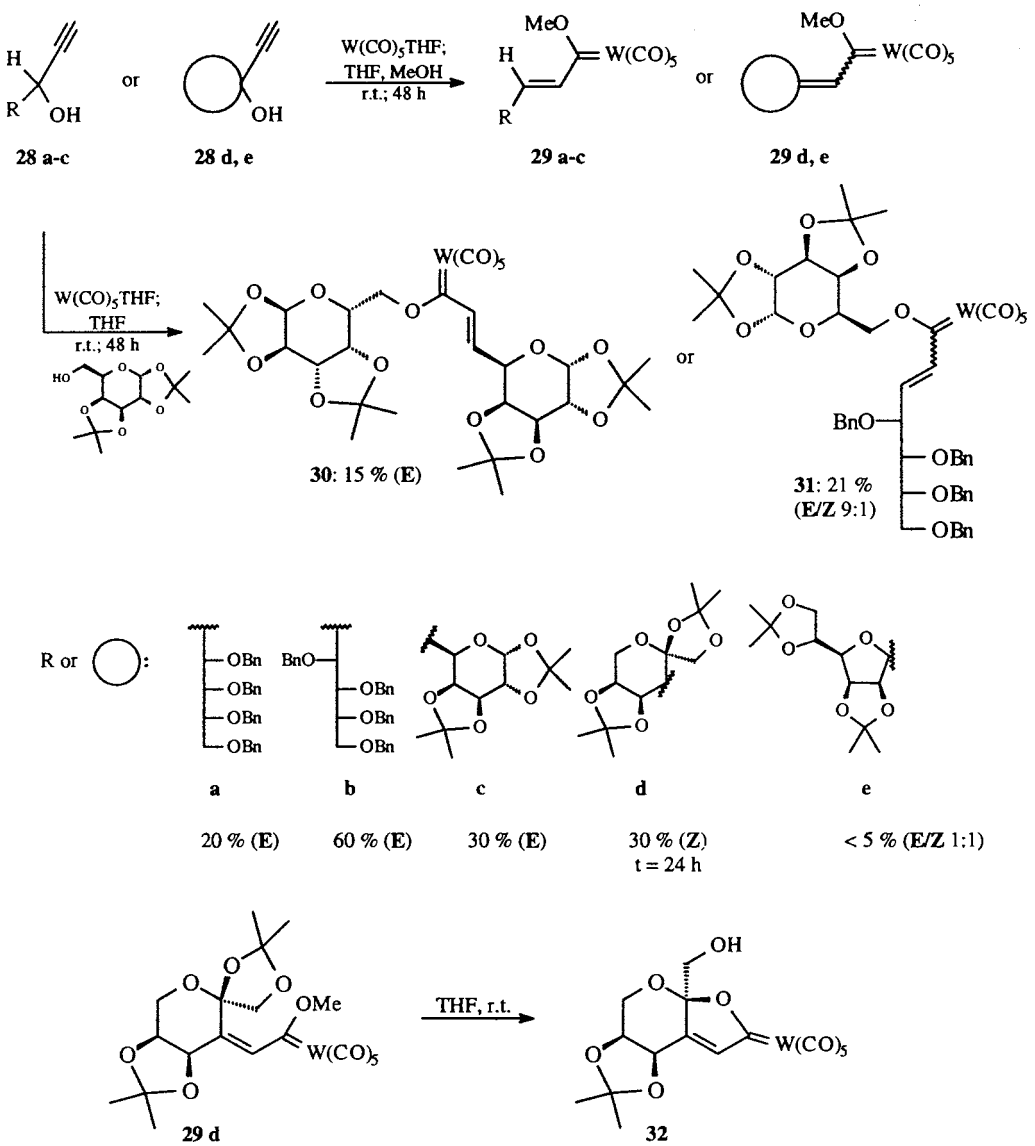
Scheme 5. Competing addition of lithioglucals to chromium carbonyl complexes.



Scheme 6. Application of vinyl chromates to stereoselective functionalization at C-2.

Above 0°C the silyl compound **17** undergoes a Ferrier-type rearrangement via elimination of trialkylsiloxide to afford the α,β-unsaturated chromium glucosylidene **21** [35]. The enolates **17**, **18** are valuable intermediates, which can be trapped by various electrophiles. Addition of hydrogen chloride in diethyl ether at low temperature resulted in the formation of the 2-deoxy complexes **22**, **23** while deuteration with d^1-TFA provided an entry to selectively labeled 2-deutero-pyranosylidenes **24**, **25**. Alkylation with allyl iodide resulted in the formation of C-2-allyl complexes **26** and **27** in good yield and with excellent diastereoselectivity (Scheme 6) [36].

Pentacarbonyl metal fragments are suitable templates for the cycloisomerization of terminal alkynols to oxacycloalkylidene complexes [37]. Carbohydrate-derived butynols have been used to synthesize a variety of metal 1,2-dideoxyglycosylidenes or carbohydrate-functionalized oxacyclopentylidene complexes [17], some of which served as chiral substrates in diastereoselective cycloaddition reactions [38]. In the presence of base at elevated temperatures the cyclisomerization can be performed catalytically to give cyclic enolethers or unsaturated carbo- and heterocycles [39], and has been recently extended to the de novo synthesis of 6-deoxy-glycals 41b. An isomerization–addition reaction sequence mediated by pentacarbonylmetal fragments [40] has been applied to the transformation of carbohydrate-derived acyclic and cyclic propynols to α,β-unsaturated metal glycosylidenes. While yields turned out to be prohibitively low in the chromium series, a number of α,β-unsaturated glycosylidene tungsten complexes, in-

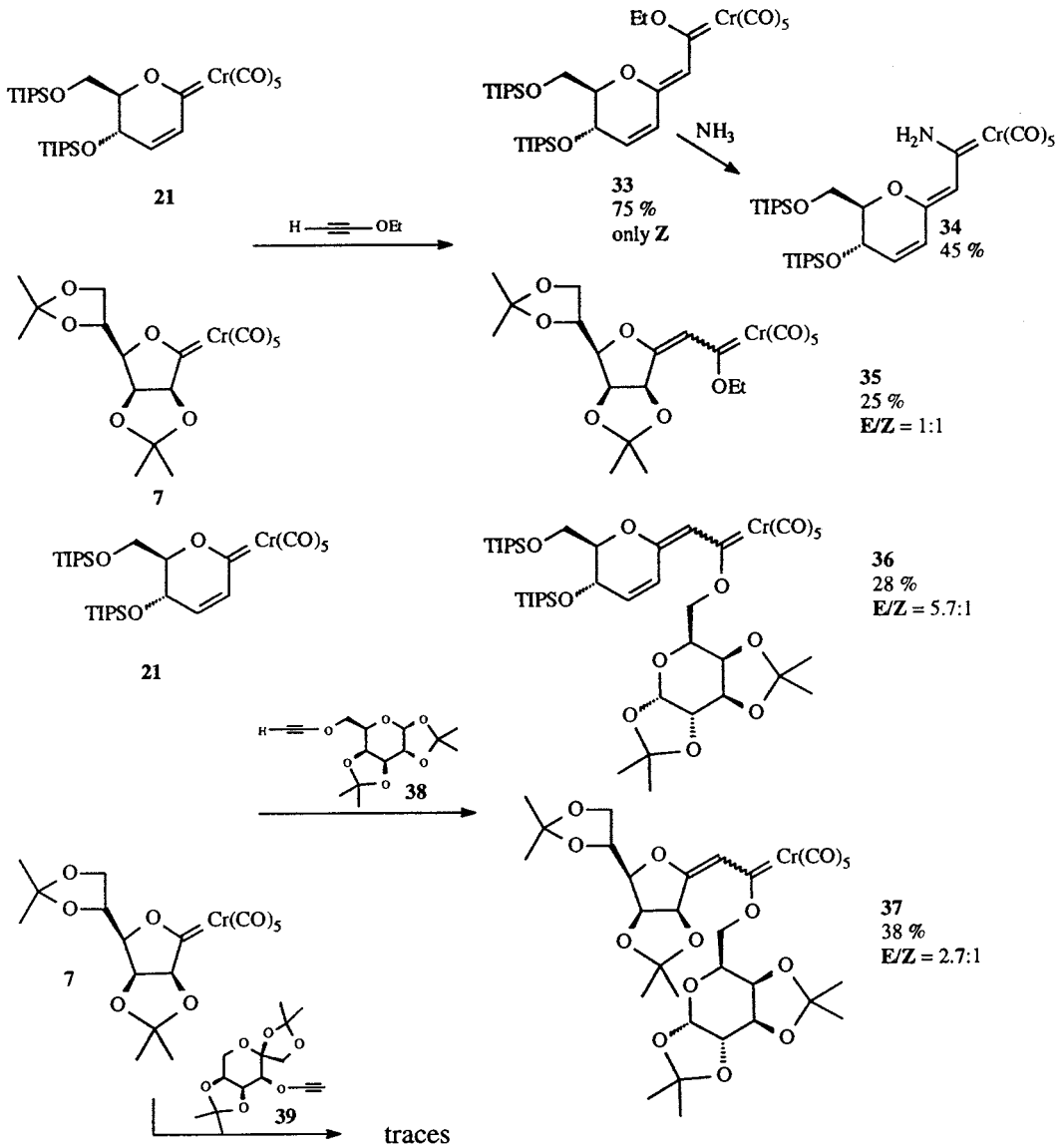


Scheme 7. Synthesis of α,β-unsaturated metal glycosylidenes from propynol-functionalized carbohydrates.

cluding disaccharide complexes **30** and **31**, have been obtained in moderate to good yield (Scheme 7) [41]. The psicose-derived propynol **28d** was modified into *Z*-vinyl carbene complex **29d** in 30% yield, and after partial deprotection, underwent cyclization to give fused vinylcarbene complex **32**.

3. Ligand-centered reactions

An alternative more straightforward route to α,β-unsaturated glycosylidene complexes such as **29e** results from a C_2-homologization based on the insertion of nucleophilic alkynes into the carbene–metal bond. The insertion proceeds smoothly with ynamines [42] and slows down with ynethers [43]; it can be further extended to cyanamides, [44] organocyanates and alkylthiocyanates [45]. Insertion of ethoxyacetylene into chromium mannofuranosylidene **7** afforded a mixture of *E*/*Z*-diastereomers of the C_2-homologuous glycosylidene complex **35** in moderate yield (Scheme 8) [46]. X-ray analysis of *E*-**35** revealed a marked push-pull character as expected from an almost perfectly planar conjugated system. The analoguous reaction of pseudoglycalylidene complex **21** with ethoxyacetylene affords a single diastereomer of dienyl(ethoxy)carbene complex **33**; NOE experiments on the ammonolysis product **34** revealed a *Z*-configuration at the exocyclic double bond [33]. The ynether insertion can be applied to the formation of organometallic disaccharides; the reaction of chromium mannofuranosylidene (**7**) with 6-*O*-ethynylgalactose (**38**) leads to a 2.7:1 *E*/*Z*-mixture of disaccharide complex **37** in which the furanose and pyranose moieties are linked by a metal carbene spacer [48]; a

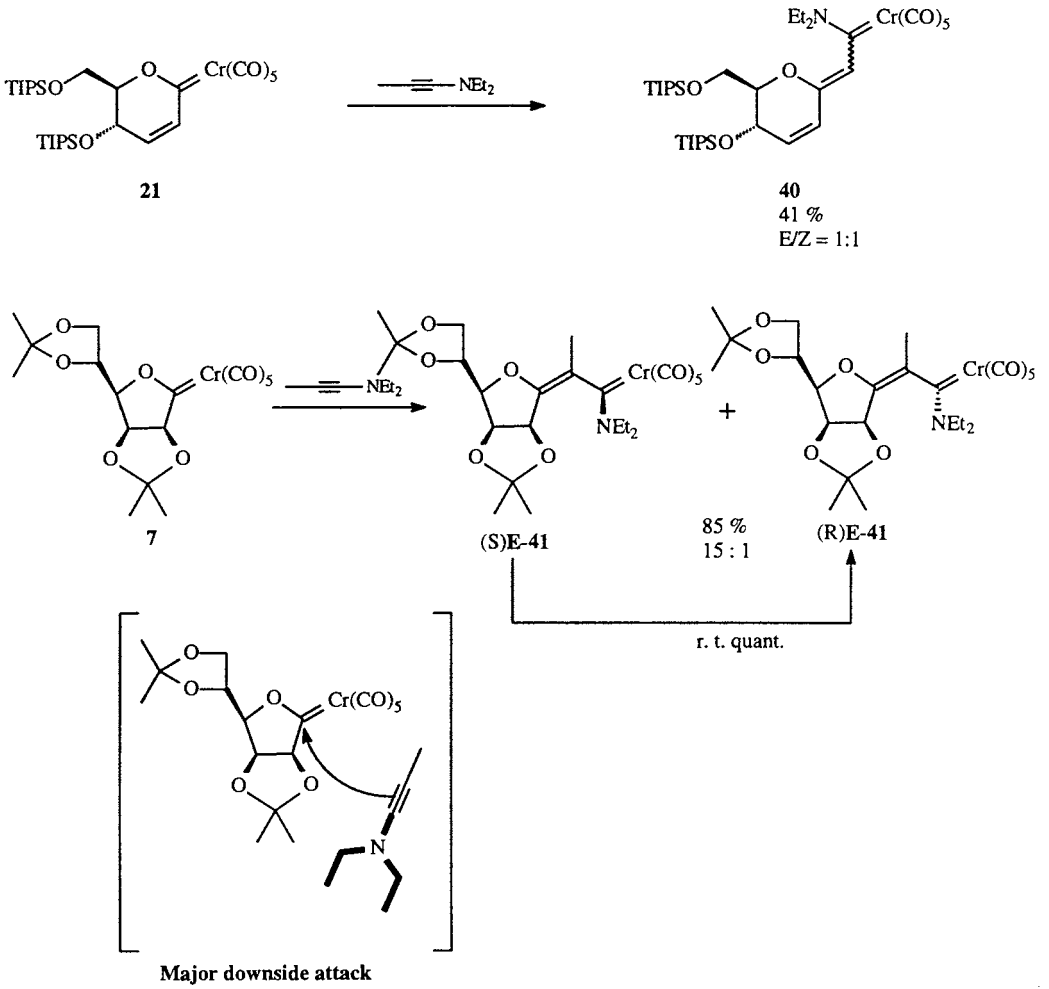


Scheme 8. C_2-Homologization of glycosylidene complexes via insertion of alkoxyacetylenes.

slightly better *E*-selectivity was observed for chromium pseudoglycalylidene **21** [47]. The insertion is hampered by decreasing nucleophilicity and increasing steric bulk of the alkyne as demonstrated by the attempted insertion of *N*,*N*-dimethyl cyanamide into **21** and **7** which failed under our standard conditions [48], and for the secondary 2-*O*-ethynylfructose derivative (**39**) which gave only traces of the insertion product although in excellent diastereoselectivity [48].

Nucleophilic ynamines are the alkynes of choice for insertive C_2-homologization. Insertion of *N*,*N*-diethylaminopropyne into chromium pseudoglucalylidene occurs under very mild conditions to give a 1:1 mixture of *E*/*Z* isomers of dienylcarbene complex **40** [50]. An excellent *E*-selectivity combined with a high chemical yield was observed for the bis(isopropylidene) protected chromium mannofuranosylidene **7** [48]. In contrast to the ethoxy analogue (**35**) the sterically more demanding diethylamino group prevents a coplanar orientation of the carbene and the alkene planes giving rise to the formation of atropisomers. Low-temperature insertion conditions led to a preferred 15:1 formation of one diastereomer **E-41** which has been characterized as atropisomer *(S)***E-41** by single crystal X-ray analysis; subsequent equilibration at room temperature resulted in a total conversion to another isomer. An NMR-study of the atropisomerization revealed a first order kinetics with an approximate activation barrier of 22 kcal mol^{-1}. The observed selectivity can be rationalized in terms of a preferred 'downside' approach of the alkyne with respect to the metal carbene bond (Scheme 9).

α,β-Unsaturated glycosylidene complexes bear a vinylic C=C double bond which is activated towards



Scheme 9. Insertion of *N*,*N*-diethylaminopropyne into glycosylidene complexes.

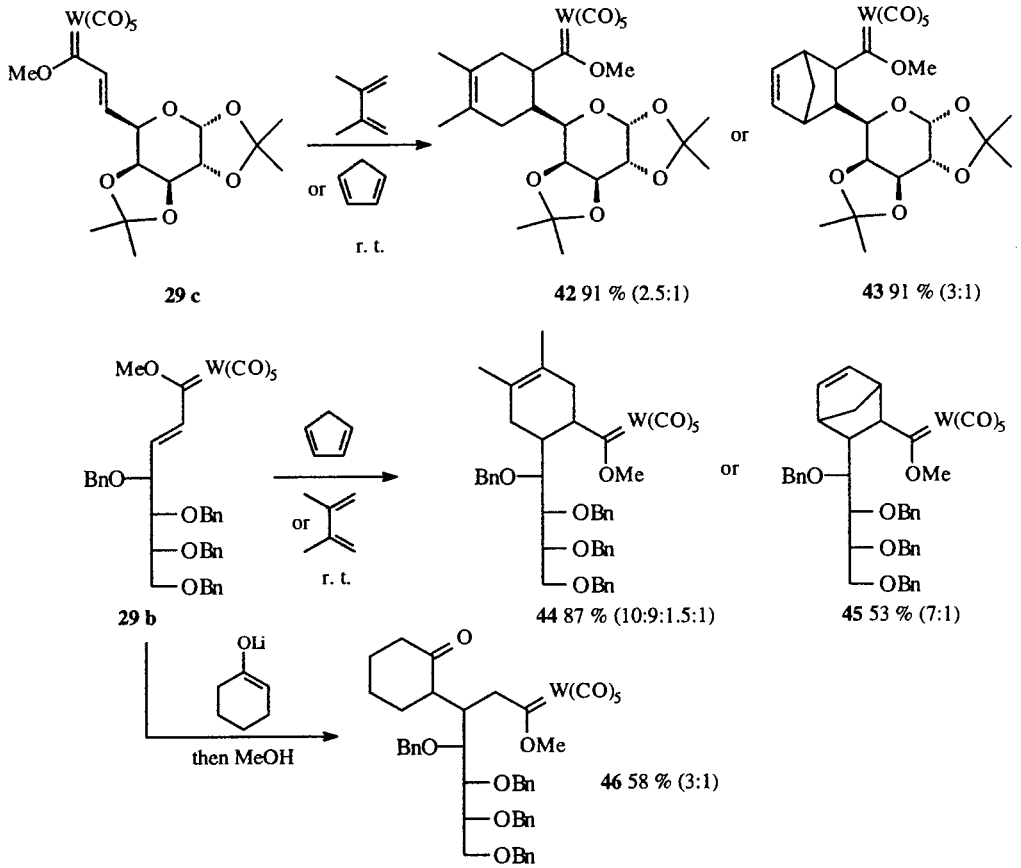
cycloaddition and nucleophilic addition reactions. Diels–Alder reactions of complexes **29b** and **29c** with cyclopentadiene or 1,3-dimethylbutadiene occur with excellent yields at room temperature; the chiral induction, however, imposed by the carbohydrate substituents generally remains only moderate and leads to a separable mixture of diastereomers from competing *re*- and *si*-face attack; an *endo*-attack was favored in all cases (Scheme 10) [43]. A similar moderate diastereoselection was observed for the conjugate addition of lithium cyclohexanone enolate to the arabinose-derived complex **29b** [43].

4. Metal-centered template reactions

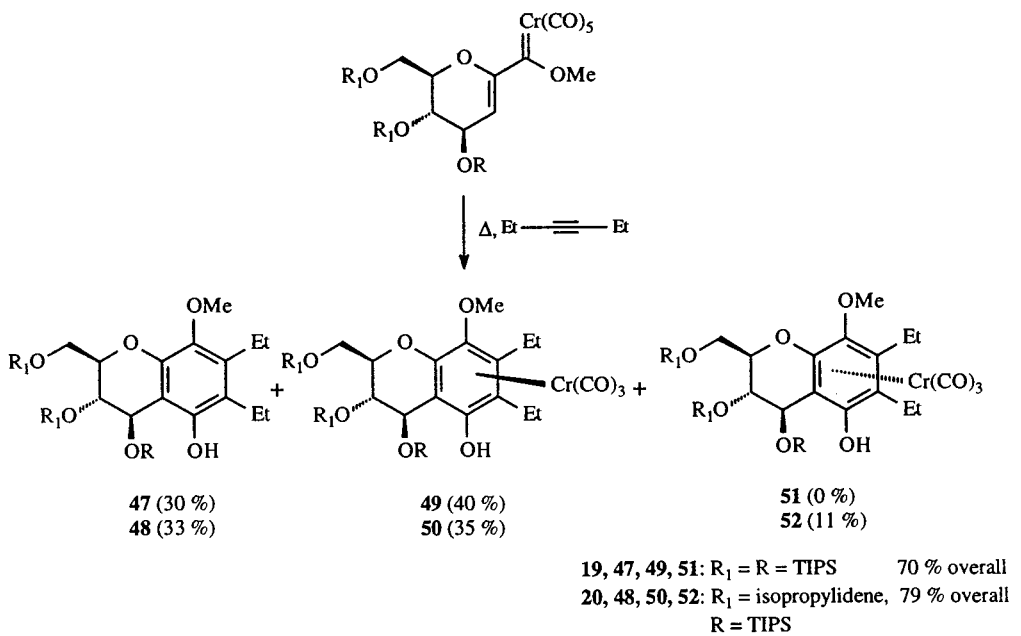
In addition to ligand-centered reactions which create new carbohydrate backbones, assisted by the metal carbene acceptor group, the metal carbonyl fragment provides a template for non-conventional cycloaddition reactions [49]. In these metal-centered transformations new carbon–carbon bonds are formed stepwise at the metal template which finally either remains coordinated to the C–C bond formation product or is released from it. If a new stereogenic element is created along the template process the carbohydrate moiety may be exploited as a chiral auxiliary to make the reaction diastereoselective.

The most useful template reaction of Fischer-type metal carbenes is the [3 + 2 + 1] benzannulation of aryl-(or vinyl)alkoxycarbene chromium complexes with alkynes 12i,j. The reaction produces densely functionalized oxygenated arenes which remain coordinated to the $Cr(CO)_3$ fragment; as a consequence of the intrinsic unsymmetric arene substitution pattern the product contains a plane of chirality which makes it an attractive intermediate for further stereoselective transformations. Diastereoselective versions of the benzannulation have been reported for chiral alkynes [50], for chiral carbene carbon side chains [51] and, more general, for chiral alcohol auxiliaries [52] in the chromium carbene.

Upon reaction with 3-hexyne glucal-derived chromium carbenes, **19** and **20** undergo benzannulation to afford highly oxygenated chromans bearing the



Scheme 10. Diels–Alder- and Michael-type reactions of α,β-unsaturated glycosylidene complexes.



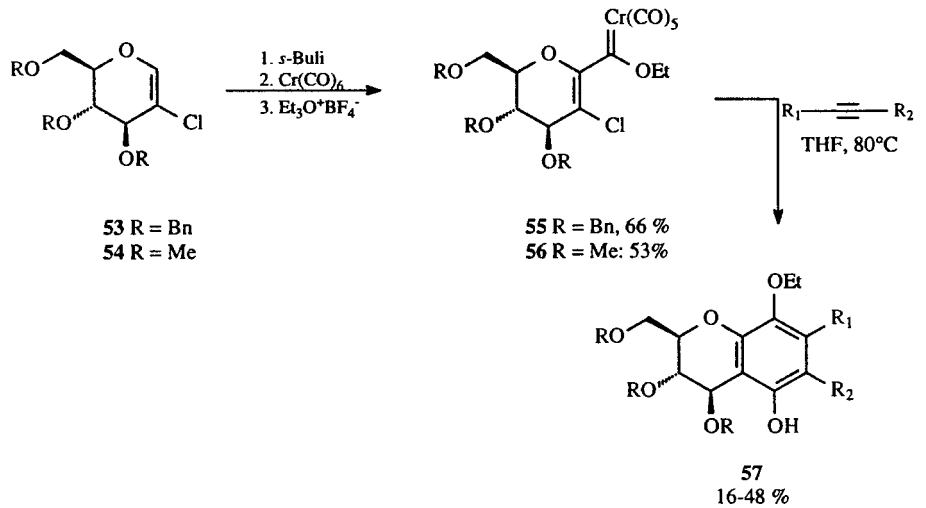
Scheme 11. Diastereoselective benzannulation of glucal-derived chromium carbenes.

$Cr(CO)_3$ fragment coordinated either from the top or the bottom face along with a minor amount of demetalated annulation product (Scheme 11). The diastereoselectivity depends on the nature of the protective groups. The TIPS-protected complex **19** produced **49** as a single diastereomer along with demetalated hydroquinone **47**

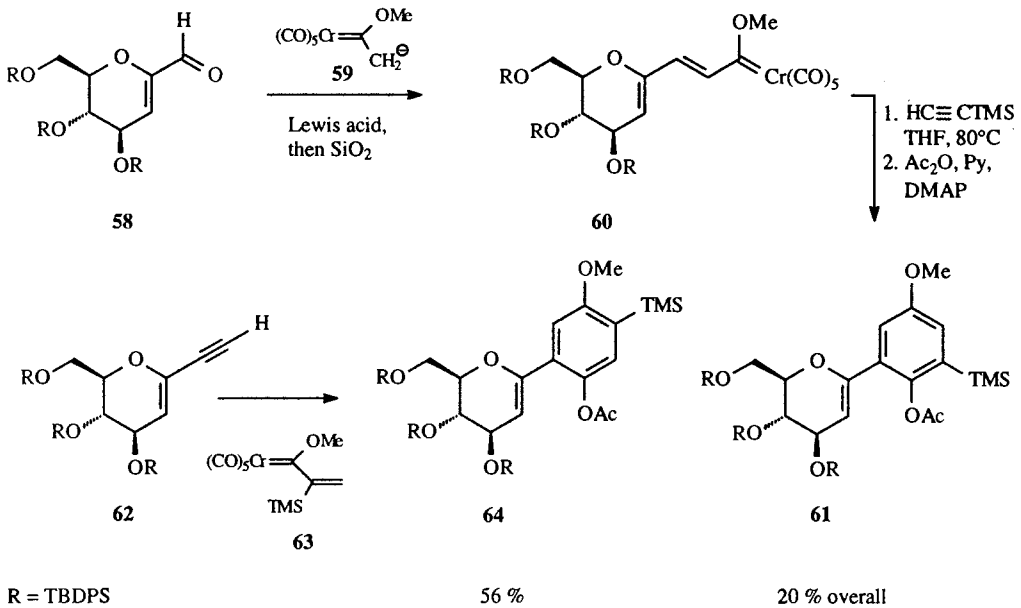
[33,53], while its isopropylidene analogue **20** gave a 3.4:1 mixture of both diastereomers **50** and **52** (d.e.: 54%) besides uncoordinated **48**. The configuration of the chiral plane has been suggested by comparative NMR-spectroscopy and finally established by X-ray analysis of **52** [55].

A similar chroman skeleton has been obtained from chlorine-substituted glucalyl carbene complexes **53** and **54** which were synthesized in moderate to good yields directly from 2-chloro-glycals [35]. Benzannulation either under thermal or dry state adsorption (DSA) conditions with various alkynes, however, did not allow to keep the $Cr(CO)_3$ fragment onto the arene; and afforded the corresponding quinones or hydroquinones (**57**) in low to moderate yields (Scheme 12).

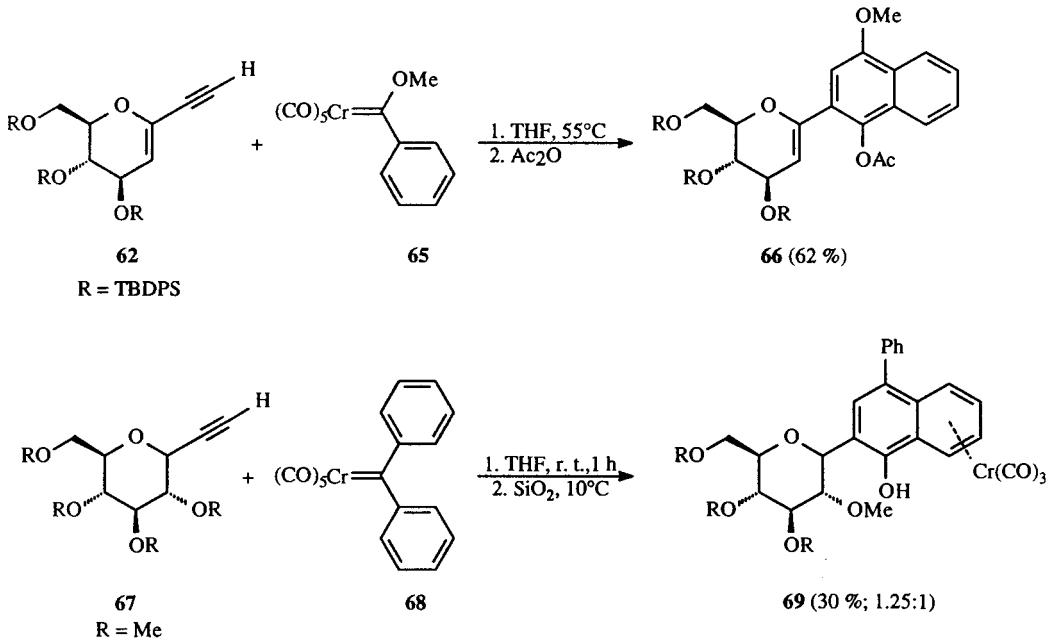
In an attempt to install the arene moiety of C-arylglycosides such as vineomycin B_2, medermycin or mederrhodin A, the glucal functionality was attached to anion **59** of [(methyl)(methoxy)carbene]pentacarbonylchromium via an aldol condensation with formylglucal **58** [54]. The resulting crude vinylcarbene complex **60** was benzannulated with TMS-acetylene followed by acylation of the phenol to afford hydroquinone **61** in 20% overall yield. A complementary approach based on the benzannulation of vinylcarbene complex **63** by the ethynylglucal **62** gave the protected hydroquinone **64** in good yield (Scheme 13). Naphthyl-*C*-glycosides are accessible from the phenyl(methoxy)carbene complex **65** [56] in an extension of this approach; the more electrophilic diphenylcarbene analogue **68** undergoes ben-



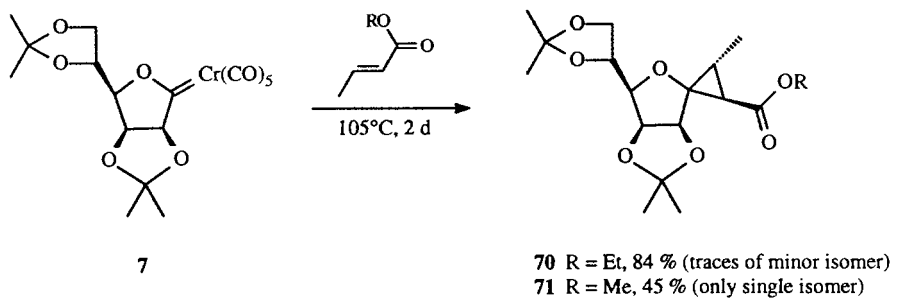
Scheme 12. Synthesis and benzannulation of 2-chloroglucalyl carbene complexes.



Scheme 13. *C*-arylglycosides via bennzannulation of vinylcarbene complexes.



Scheme 14. Hydroxynaphthyl *C*-glycosides via benzannulation.



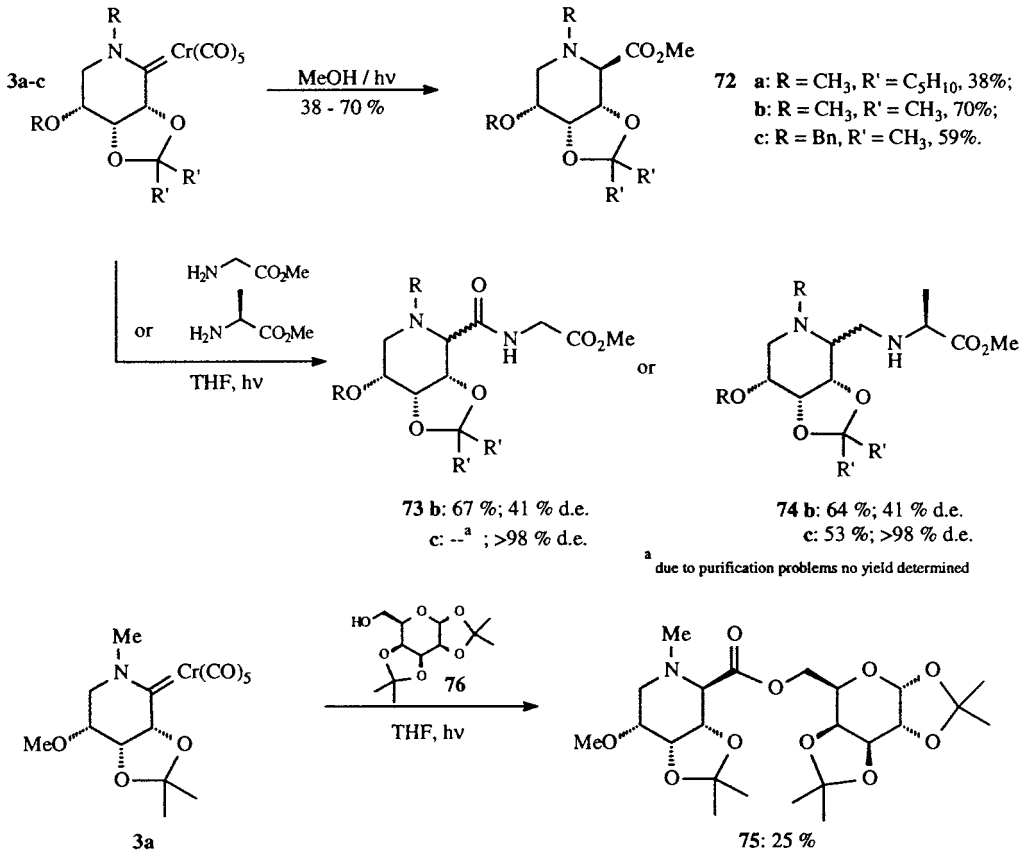
Scheme 15. Cyclopropanation of electron-deficient alkenes with glycosylidene complexes.

zannulation under very mild conditions below room temperature which allows to keep the $Cr(CO)_3$ fragment in the *C*-naphthol glycoside although in low diastereoselection (Scheme 14) [55].

Besides benzannulation with alkynes the chromium carbonyl template also effects cyclopropanation of alkenes by Fischer-type carbene complexes [56]. Activated alkenes undergo a diastereoselective [2 + 1] cycloaddition by glycosylidene complexes to give donor-acceptor substituted spirocyclopropanes as illustrated for chromium mannofuranosylidene (**7**) (Scheme 15) [57].

The chromium carbonyl fragment assists the photogeneration of ketene equivalents by an intramolecular carbonylation of the carbene ligand. This methodology has been developed by Hegedus [58] for various applications in natural product synthesis, especially β-lactams, α-amino acid esters and dipeptides 12r. Appropriate photoconditions generate ketene equivalents from iminopyranosylidene complexes (Scheme 16). These intermediates can be trapped by *N*- and *O*-nucleophiles with high β-stereoselectivity to give C_1-elongated imino aldonic esters and amides [25b,29]; amino acids as *N*-nucleophiles stereoselectively lead to carbopeptides. The selectivity depends on the *N*-substituent on the iminosugar moiety; *N*-benzyl substitution significantly increases the selectivity over *N*-methyl groups [59]. With less pronounced *O*-nucleophiles such as the galactose derivative **76** the addition proceeded significantly slower and provided the β-imino-pseudodisaccharide **75** in somewhat lower yield.

While the yield clearly reflects the different steric demand of either *N*- and *O*-protecting groups, the stereochemical outcome seems to be controlled by the intermediate complexation of the ketene by the tetracarbonyl chromium fragment which preferentially occurs from the face opposite to the isopropylidene protecting groups (*re*-face). Thus, the addition of the nucleophile and the protonation occur selectively from the *si*-face (i.e. bottom face) directing the carbonyl



Scheme 16. Photoinduced synthesis of methyl 2,6-imino-D-allonates.

substituent to the β-position. This rationale is supported by the observation that the β-selectivity decreases when THF is replaced as solvent by the better coordinating acetonitrile.

5. Conclusions

Different and complementary methodologies for the synthesis of Fischer-type metal glycosylidenes have been developed in the recent past, and now allow the incorporation of the versatile metal carbene functionality into various carbohydrate backbones. They afford synthetically useful yields on a preparative scale. Glycosylidene complexes can be handled with standard organometallic techniques; some of them even tolerate air and water for a limited period of time. They undergo ligand-centered reactions which benefit from the metal carbene fragment as an organometallic functional acceptor group and create new carbohydrate backbones while the metal carbene functionality is maintained and available for further carbon–carbon bond formation. In addition, metal-centered reactions such as benzannulation, cyclopropanation and ketene formation are compatible with glycosylidene ligands. Although the carbohydrate skeleton provides a series of consecutive stereocenters, subsequent reactions of glycosylidene complexes often proceed with only moderate diastereoselectivity so far. Preliminary experiments suggest that the selectivity may be increased by an appropriate choice of the protective groups, which play a crucial role in the conformation of carbohydrates. Metal glycosylidenes undergo stereocontrolled ring opening–recyclization reactions, exhibit considerable α-CH acidity, and thus offer new perspectives for *C*-glycosidation and for organometallic analogues of disaccharides and glycoconjugates.

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