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Transition metal catalyzed neoglycoconjugate syntheses*

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Abstract: Carbohydrate-containing clusters of various valency were synthesized using transition metal-catalyzed reactions. Thus, Grubbs' ruthenium benzylidene catalyst was used successfully in olefin self-and cross-metathesis reactions from both O-and C-alkenyl glycopyranosides. The reaction was also used to generate C-linked pseudodisaccharides. Oxidative dimerization of terminal alkynes such as 2-propynyl glycopyranosides was accomplished with palladium and copper-catalyzed homo-and cross-coupling reactions. Sonogashira-type cross coupling between 2-propynyl and 4-iodophenyl mannopyranosides afforded novel sugar-rods useful in studying carbohydrate–protein interactions. Cyclotrimerization of terminal as well as symmetrical alkyne derivatives with dicobalt octacarbonyl allowed access to trimers and hexamers, respectively.

INTRODUCTION

Carbohydrate–protein interactions are at the origin of a wide range of biological phenomena that span from cell-growth to fertilization through cancer cell metastases [1]. Unfortunately, individual binding interactions are characterized by low affinities. Nature has however, developed an opportunistic compensating strategy by offering interacting partners, i.e. both proteins and carbohydrates, multivalent binding sites, thus offering several simultaneous anchoring positions. From the carbohydrate standpoint, multivalency is imparted by mobile glycolipids that form patches on the cell surfaces and by multiantennary glycoproteins, mucins, or proteoglycans [2]. While small oligosaccharide fragments constitute weak inhibitors in the above interactions, multivalent neoglycoconjugates have demonstrated enhanced potency through increased avidity [3]. Such neoglycoconjugates offer great promises as anti-adhesins toward pathogenic infections [4]. Moreover, there are increasing evidences that well organized cross-linked lattices can form when multivalent protein receptors are admixed with naturally occurring multiantennary glycans [5] or synthetic glycodendrimers [6]. It has also been previously demonstrated that this phenomenon can even occur with synthetic carbohydrate dimers [7]. All of the above evidences support the notion that small-rigidified carbohydrate clusters bearing hydrophobic residues would form stable complexes. To further expand methodologies to generate families of oligomeric carbohydrate clusters ('sugar-rods'), transition metal catalyzed syntheses will be described.

OLEFIN METATHESIS WITH TRANSITION METAL

Ruthenium catalyzed alkenyl glycoside homodimerization

In recent years, transition metal catalyzed olefin metathesis has gained increasing interest in organic syntheses [8]. Stable Grubbs' ruthenium carbene complex **1** [9] and air sensitive Schrock's molybdenum complex **2** [10] are especially noteworthy. Ruthenium and molybdenum carbenoids have been recently

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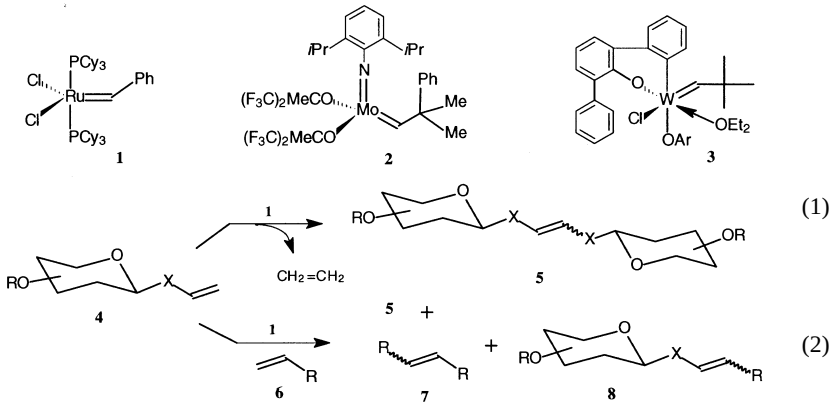
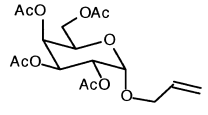
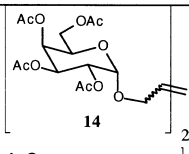
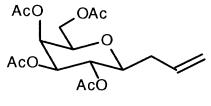
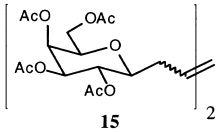
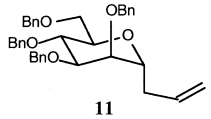
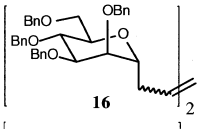
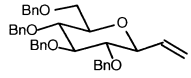
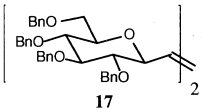
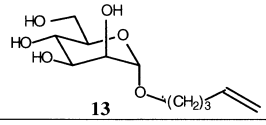
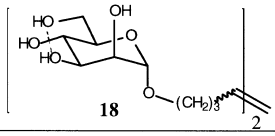
used in carbohydrate-related ring-closing metathesis (RCM) [11], cross-metathesis (CM) [12] and ring-opening metathesis (ROM) [13] reactions. Carbohydrates homodimerization (eqn 1) was first reported using tungsten aryloxoalkylidene complex **3** [14]. However, these conditions were unsuccessful with O-allyl glycosides as well as benzyl-protected sugar derivatives (Scheme 1).



Scheme 1

Recent developments in our laboratory have showed that O-allyl, O-pentenyl, C-vinyl, and C-allyl glycopyranosides (**4**) can undergo efficient homodimerizations (eqn 1) in refluxing dichloromethane in the presence of either Grubbs' or Schrock's catalyst [15]. Given the need to work under Schlenk's conditions with catalyst **2**, Grubbs' catalyst **1** was used throughout. Acetate (**9** and **10**) and benzyl (**11** and **12**) protecting groups are compatible with the mild reactions conditions and even unprotected carbohydrate derivatives (**13**) can be transformed into dimers (**18**). With the exception of C-vinyl glycopyranoside (**12**), which provided **17** in low yields (24%) but recoverable starting materials, the reactions afforded stereoisomeric *E/Z* mixtures ranging from 1:1 to 5:1 in favor of the more thermodynamically stable *E* isomers (Table 1). Interestingly, only a catalytic amount of the transition metals was necessary since

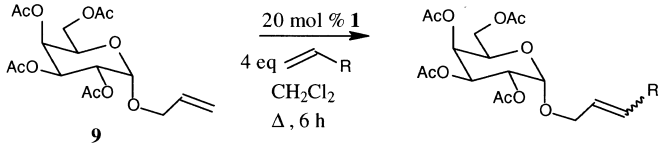
Table 1 Olefin self-metathesis of representative alkenyl O-and C-glycopyranosides

Substrate	Homodimer	(*E/Z*)	Yield (%)
 **9**	 **14**	(5/1)	92
 **10**	 **15**	(1/1)	75
 **11**	 **16**	(1/1)	83
 **12**	 **17**	(100/0)	24
 **13**	 **18**	(1.3/1)	67

methylidene carbenoids are generated in the catalytic cycle after the initial release of styrene. Presumably, the exclusive formation of the *E* homodimer **17** obtained from vinyl glycoside **12** arose from steric hindrance since homologous C-allyl glycopyranosides **10** and **11** afforded high conversion into **15** and **16** but equimolar ratios of *E/Z* isomers. The resulting homodimers could be readily reduced into single saturated products or separated by HPLC. In preliminary lectin binding microturbidimetric experiments with Concanavalin A, unprotected dimeric mannopyranosides were poor or noncrosslinkers, thus showing improper intersugar distances or lack of appropriate rigidity.

Ruthenium catalyzed alkenyl glycoside cross-metathesis

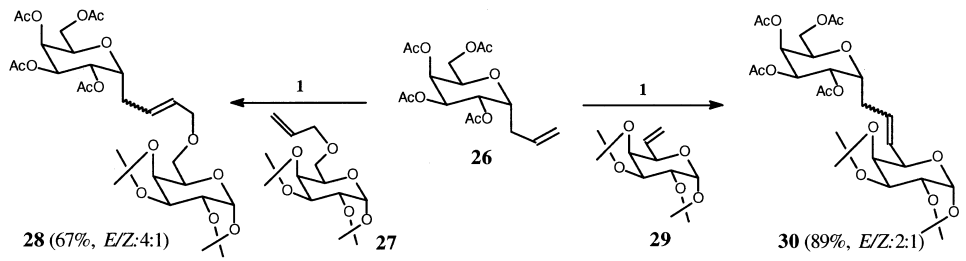
Early observations from the above experiments revealed that the small amount of styrene initially released from catalyst **1** could reenter into the catalytic cycle to form cross-metathesis products (eqn 2). Metal carbene catalyzed intermolecular coupling may yield three different types of alkenes: the desired cross-metathized glycosides (**8**) and two undesired homodimers originating from self coupling of the other two partners (**5** and **7**). With the exception of acrylonitrile, allylsilane and stannane, selective cross-metathesis has not found widespread application in organic synthesis [8]. If suitable cross-metathesis conditions can be found, the strategy could be exploited to expand the usefulness of O-/C-allyl glycosides as 'spacers' in neoglycoconjugate preparation [16]. To further explore the scope and limitations of the Grubbs' catalyst in cross-metathesis reactions, a series of model experiments were effected using various alkenes (**6**). To drive the reactions toward the desired cross-metathized product (**8**), dilute solutions were used together with at slight excess (2–4 equiv.) of the added alkenes **6** [17]. Unsurprisingly, allyltrimethylsilane and styrene gave excellent yields. The reactions were thus applied to alkenes bearing masked alcohol, acid, and amine functionalities (Scheme 2). Model O-allyl α-D-galactopyranoside **9** was treated with a wide variety of alkenes of type **6** to produce cross-metathized products **19–25** in good to excellent yields and stereoselectivity ranging from 2:1 to 97:3.



19 R = CH_2SiMe_3 (94%, *E/Z:* 4:1) **20** R = $CH_2CH_2CO_2Me$ (67%, *E/Z:* 2:1)
21 R = CH_2OTBS (69%, *E/Z: 95*:5) **22** R = Ph (80%, *E/Z: 97*:3)
23 R = Ph-4-OAc (75%, *E/Z: 95*:5) **24** R = CH_2NHCbz (65%, *E/Z: 4*:1)
25 R = CH_2NHBoc (57%, *E/Z:*4:1)

Scheme 2

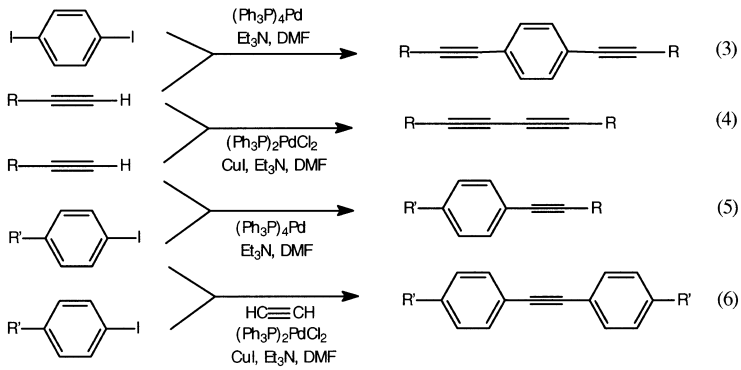
The success encountered in this approach prompted us to construct heterobifunctional dimers. However, instead of the head to head condensation approach discussed above, a head to tail cross coupling was envisaged. In this way, C-linked pseudodisaccharides could be contemplated (Scheme 3). For instance, when C-allyl α-D-galactopyranoside (**26**) was treated with either 2 equiv. of 6-O-allyl **27** or 6-vinyl derivatives **29** and Grubbs' catalyst **1**, heterodimers **28** and **30** were obtained in 67% and 89% yields, respectively. These molecules offer great potential as glycomimetic precursors and work is ongoing toward this goal.



Scheme 3

PALLADIUM AND COPPER(I)-CATALYZED ARYL AND ALKYNYL GLYCOSIDE CROSS-COUPLING

As mentioned above, it was deemed advantageous to construct sugar-rods having constrained conformational mobility while combining elements of hydrophobicity. To this end, it was decided to incorporate aryl and alkynyl residues as tethering units between dimeric clusters. Equations 3–6 (Scheme 4) show representative strategies toward these goals. For instance, propynyl glycosides could be dimerized around diiodobenzene using tetrakis(triphenylphosphine)palladium(0) under Sonogashira cross-coupling conditions [18] (eqn 3). Alternatively, the same propynyl glycosides could be oxidatively dimerized under Glaser's conditions (CuI, O_2, pyridine) [19], Eglinton's conditions ($Cu(OAc)_2$, pyridine) [20], or simply by treatment with catalytic amount of bis(triphenylphosphine)palladium dichloride and cuprous iodide [21] (eqn 4). Additionally, heterodimers could be obtained from propynyl glycosides and iodophenyl glycosides (eqn 5) under Sonogashira conditions and finally, two iodophenyl glycosides could be simultaneously tethered on acetylene gas under the above conditions (eqn 6).



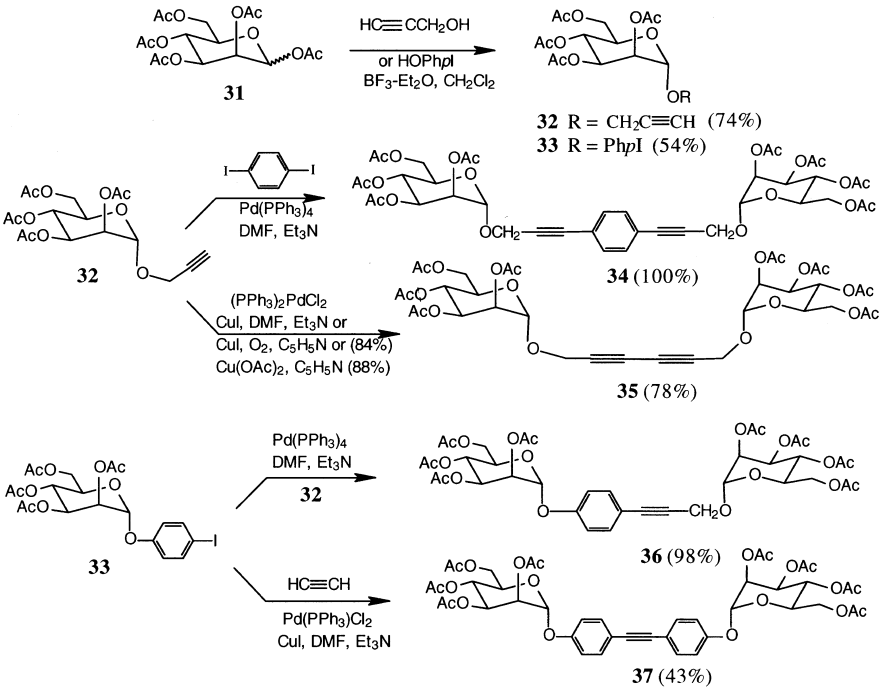
Scheme 4

All of the above strategies were met with success using several monosaccharides and disaccharides. For sake of clarity and given our vested interest toward mannopyranosides, the following discussions will be centered around that particular carbohydrate ligand since it is involved as host cell receptor in urinary tract infections by type 1 fimbriated *Escherichia coli* [22]. The required peracetylated 2-propynyl (**32**) and 4-iodophenyl (**33**) α-D-mannopyranosides were readily prepared under standard conditions using Lewis-acid catalyzed glycosidations of peracetylated mannopyranose **31** with either propargyl (74%) or 4-iodophenyl (54%) alcohol (Scheme 5). Treatment of **32** (2.2 equiv.) with 4-diiodobenzene (1 equiv.) and $(Ph_3P)_4Pd$ (10 mol%) (DMF-Et_3N, 1:1; N_2, 60 °C, 3.5 h) afforded peracetylated dimer **34** in essentially quantitative yield while treatment with 1.1 eq of cuprous iodide and $(Ph_3P)_2PdCl_2$ (10 mol%) (DMF-Et_3N, 1:2.5; r.t., 1 h) afforded diyne **35** in 78% yield. Similar results were also obtained using cuprous iodide (pyridine, r.t., O_2, 3 h) (84%) [19] or cupric acetate (pyridine, 80 °C, 3 h) (88%) [20].

Under Sonogashira cross-coupling conditions, 2-propynyl (**32**) and 4-iodophenyl (**33**) mannopyranosides provided unsymmetrical dimer **36** in 98% yield. Symmetrical disubstituted alkyne such as **37** was obtained in 43% yield from aryl iodide **33** when treated with acetylene gas and $(Ph_3P)_2PdCl_2$/CuI. Transesterification of **34**–**37** under Zemplén conditions (NaOMe, MeOH) afforded the corresponding fully deprotected sugar-rods having good to excellent water-solubility. Some of these compounds showed high cross-linking properties when mixed with tetrameric plant lectin such as Concanavalin A [23].

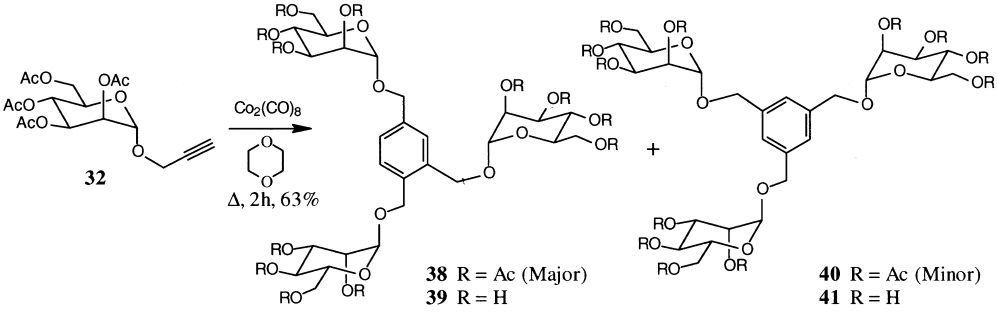
DICOBALT OCTACARBONYL CATALYZED ALKYNYL GLYCOSIDE CYCLOTRIMERIZATION

Amongst various dendritic mannopyranosides previously tested for their inhibitory potency against type 1 fimbriated *E. coli* binding to yeast mannan, it was found that those containing three ligand residues were substantially better than larger clusters made of up to 16 mannosides [22]. Pioneering observations [24] on 'artificial antigens' having antibody cross-linking ability strongly suggest that analogous trimeric



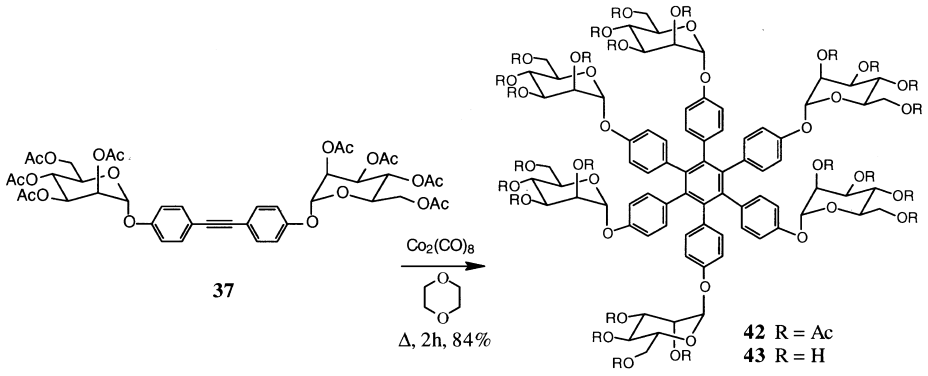
Scheme 5

ligands built on aromatic core may also show the required properties. Another more recent study by Kaufman & Sidhu [25] demonstrated that aryl cluster glycosides could be constructed by a one step cyclotrimerization of 2-propynyl glycosides using dicobalt octacarbonyl ($Co_2(CO)_8$), albeit in low yields and long reaction time. Classical studies by Vollhardt [26] showed that dicarbonyl(η^5-cyclopentadienyl)cobalt ($CpCo(CO)_2$) could also provide cobalt-mediated alkyne [2+2+2]-cycloadditions. Based on these observations, we initially attempted comparative reactivity between the above two cobalt catalysts in cyclotrimerization of alkyne **32**. Surprisingly, dicobalt octacarbonyl was far more superior than the corresponding cyclopentadienyl catalyst. For instance, treatment of **32** in refluxing dioxane for only 2 h (compared to 21 days [25]) afforded the expected regioisomeric mixture of **38** and **40** in 63% yield and in a 10:1 molar ratio, respectively (Scheme 6). The reaction was general and equally applied to several other saccharides [27]. Interestingly, we also demonstrated for the first time that Grubbs' catalyst **1** could give similar results [28]. Attempts to use other rhodium or palladium catalysts failed to provide such trimers. Obviously, these clusters could also be synthesized using more classical glycosylation chemistry. Thus, a recent report described the syntheses of analogous derivatives using Lewis-acid-catalyzed glycosydation of glycals with 1,3,5-benzenetrimethanol [29].



Scheme 6

Prompted by the success of the dicobalt octacarbonyl-catalyzed cyclotrimerization, we next attempted to perform similar reactions with symmetrical alkyne **37**. Under identical conditions described above, **37** gave hexamer **42** in 84% yield (Scheme 7). De-O-acetylation of **42** under Zemplén conditions provided water-soluble **43** in quantitative yield. The reaction failed with ruthenium alkylidene **1**. The scope and limitation of this fascinating process are now being investigated with other sugars, including oligosaccharides. Interestingly, 'molecular asterisk' **43** already showed excellent cross-linking properties with plant lectins, showing that the spacial orientation and rigidity provided by the aryl core offer great potential as neoglycoconjugates. The effects of the spacer-arm and the outer aromatic core are also being evaluated for binding optimization.



Scheme 7

CONCLUSION

Transition metal catalyzed olefin homo- and cross-metathesis reactions have been successfully applied to carbohydrate derivatives to generate a wide range of modified neoglycoconjugates of great potential in glycobiology. Grubbs' catalyst in particular offers the advantage of being compatible with most protecting groups normally utilized in carbohydrate chemistry. Although, the procedure affords mixtures of *cis* and *trans* stereoisomers, the resulting metathized products could be separated by HPLC techniques or simply reduced to a single saturated form. The strategy is also useful for the preparation of C-linked pseudo-disaccharides. When palladium catalysts are used with aryl iodides and terminal alkynes, it is possible to generate water-soluble 'sugar-rods' in high yields. The procedure is general and also compatible with various sugar structures and protecting groups. The end products possess the necessary rigidity and lipophilicity to be used as cross-linking materials in the study of carbohydrate–protein interactions. Some of these derivatives have been shown to form insoluble precipitates with tetravalent phytohemagglutinin Concanavalin A isolated from the plant *Canavalia ensiformis* and X-ray measurements are being performed. When the analogous terminal or internal alkynyl glycosides were treated with dicobalt octacarbonyl, trimeric as well as hexameric glycoclusters were formed in good to excellent yields.

ACKNOWLEDGEMENTS

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