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FULL PAPER

Acid-Assisted Direct Olefin Metathesis of Unprotected Carbohydrates in Water

Brian J.J. Timmer[a] and Olof Ramström*[a,b,c]

Abstract: The ability to use unprotected carbohydrates in olefin metathesis reactions in aqueous media is demonstrated. Using water-soluble amine-functionalized Hoveyda-Grubbs catalysts under mildly acidic aqueous conditions, the self-metathesis of unprotected alkene-functionalized α-D-manno- and α-D-galactopyranosides could be achieved through minimization of non-productive chelation and isomerization. Cross-metathesis with allyl alcohol could be also be achieved with reasonable selectivity. The presence of small quantities (2.5 vol%) of acetic acid increased the self-metathesis product formation while significantly reducing the alkene isomerization process. The catalytic activity was furthermore retained in the presence of large amounts (0.01 M) of protein (BSA), underlining the potential of this carbon-carbon bond forming reaction under biological conditions. These results demonstrate the potential of directly using unprotected carbohydrate structures in olefin metathesis reactions under mild conditions compatible with biological systems, thereby enabling their use in, *e.g.*, drug discovery and protein derivatization.

Introduction

The formation of carbon-carbon bonds remains a coveted transformation in chemistry and is generally required to build basic architectures of organic molecules and materials. One of the methods devised to accomplish this, olefin metathesis,[1–3] is in this context highly useful since it results in efficient formation of new carbon-carbon double bonds under catalytic conditions. The scientific impact of this method has been exceptional, leading to a large number of applications in many areas, such as organic synthesis, materials science, energy research, molecular topology, and medicinal chemistry.[4–9] The reaction is furthermore of dynamic nature, an attractive feature that has been adopted to generate, *e.g.*, dynamic systems, complex architectures, and self-healing materials.[10–20]

Ever since the introduction of the olefin metathesis reaction, much effort has been invested in improving the catalysts. This has, *e.g.*, resulted in the appearance of commercially available and bench-stable catalysts,[21–25] *Z*-selective catalysts,[26–28] and highly active catalysts for ethenolysis.[29,30] However, while the use of olefin metathesis in organic solvents has been extensively demonstrated, applications in aqueous media have been considerably less explored.[31] The majority of biologically interesting structures, such as unprotected peptides and carbohydrates, have therefore been largely incompatible with the reactions. To address this limitation, several strategies to enable olefin metathesis in aqueous media have been proposed, including the use of biphasic systems,[32] immobilized catalysts,[33,34] nanoreactors and micellar catalysis,[35–39] artificial metallo-enzymes,[40] as well as modifications of the catalysts or the reaction conditions to increase the reactivities.[41–50] Unfortunately, many of these systems are either incompatible with water-soluble substrates or present a very narrow substrate scope.[31,51,52]

The olefin metathesis reaction has nevertheless been applied to the carbohydrate substance class to some extent,[53] in these cases generally using protected structures in organic solvents. However, the direct use of unprotected carbohydrates in aqueous media would significantly increase the application range to biological systems and other situations where water is desired as solvent. Pioneering studies of the groups of Davis,[54–56], Harding,[57], as well as Cai and Yu,[58] show that unprotected carbohydrates can be used as reactants in olefin metathesis transformations in mixed solvent systems. Using Hoveyda-Grubbs 2nd-generation catalyst in *tert*-butanol-water mixtures, selective coupling of carbohydrates to proteins could thus be achieved. In these cases, however, privileged alkenes carrying allylic chalcogen atoms and high catalyst loadings were generally required, thereby limiting the application range. Moreover, the group of Blechert reported that self-metathesis of a *C*-glycoside mainly resulted in isomerization rather than the desired dimerization.[34]

In this study, we have addressed the challenge of applying olefin metathesis to unprotected carbohydrate structures in aqueous media. Inspired by previous studies on metathesis and persistent carbenes, we hypothesized that the introduction of morpholinium groups on an *N*-heterocyclic carbene (NHC) ligand would result in high, overall solubility of the catalyst, thereby resulting in improved catalytic efficiencies in water phase. In addition, since the ruthenium carbenoid species would involve the carbohydrate structures during the reaction, homogeneous catalysis would be ensured throughout the process. Using this design, we applied the catalysts to self- and cross-metathesis involving a range of alkenyl glycosides, and furthermore evaluated the effects of a weak Brønsted acid on the reactions.

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Results and Discussion

The catalysts were designed to contain two tertiary or quaternary amines, introduced symmetrically at both ends of an imidazolidine-based NHC core. Installation of the quaternary amine centers was furthermore devised by late stage methylation of the non-methylated catalyst structure, allowing for easier synthesis and purification.[47] Synthesis of carbene precursors matching similar criteria has been reported by Plenio and coworkers,[59] and an analogous strategy was adopted in the present case (Figure 1). Thus, electrophilic aromatic substitution between 2,6-dimethylaniline and the morpholinium ion of formaldehyde first yielded morpholine-substituted aniline **1**. Treatment of this compound with glyoxal provided diimine **2**, which upon reduction with lithium aluminum hydride yielded the corresponding 1,2-diamine **3**. Subsequent ring closure of this species using triethyl orthoformate in the presence of ammonium chloride provided imidazolinium chloride **4**, serving as the NHC ligand precursor. Deprotonation of compound **4** with KHMDS yielded the *N*-heterocyclic carbene, which could then be directly coupled to Hoveyda-Grubbs 1st-generation catalyst to provide non-methylated catalyst **C1**. Finally, straightforward methylation of the morpholine moieties with methyl triflate provided catalyst **C2** in six steps from commercially available starting materials.

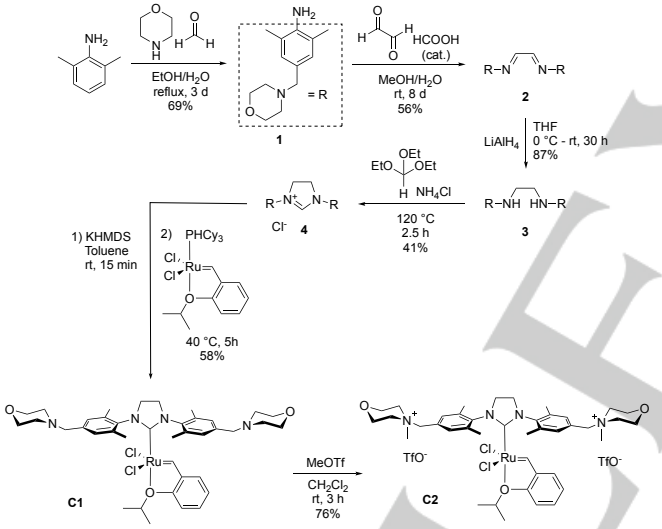
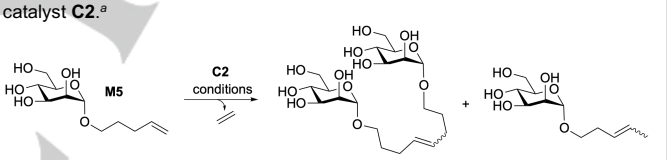


Figure 1. Synthesis of catalyst **C2**.

Catalyst **C2** was first applied to the potential self-metathesis of two unprotected carbohydrates: allyl α-D-mannoside (**M3**) and 3-butenyl α-D-mannoside (**M4**, cf. structures in Table 2). Unfortunately, no self-metathesis occurred for either mannoside in the presence of 2.5 mol% catalyst in D_2O at 40 °C and 0.1 M initial substrate concentration, and only alkene isomerization was observed in both cases. Interestingly, only single isomerization to the 2-butenyl isomers was observed for the 3-butenyl species, a result incidentally also observed for all other tested reactants (*vide infra*). However, when applying the catalyst to 4-pentenyl α-D-mannoside (**M5**), carrying a longer olefinic aglycone, some self-metathesis product could be observed (Table 1, entry 1). In this case, increasing the temperature to 50 °C or 60 °C did not improve the amount of self-metathesis product, but only led to faster decomposition of the catalyst and higher isomerization rates (Table 1, entries 2-3). On the other hand, doubling the catalyst loading to 5 mol% resulted in an increase in the formation of self-metathesis dimer to 13%, however also associated with a higher formation of isomerization products (Table 1, entry 4).

Based on previous observations by Grubbs and coworkers,[60] the possibility to increase the metathesis conversion by carrying out the reaction under slightly acidic conditions was next explored. Interestingly, addition of 2.5 vol% acetic acid not only increased the formation of the self-metathesis product, but the isomerization rate was at the same time significantly reduced (Table 1, entry 5). This reduced isomerization effect, previously shown in organic solvents for this additive,[61] was presumed to be due to quenching of potential ruthenium hydride species formed in the reaction. However, the acid concentration proved sensitive to the performance, and increasing the concentration of acetic acid to 5 vol% resulted in reduced self-metathesis (Table 1, entry 6), while neat acetic acid completely quenched any reactivity. These results suggest that acetic acid temporarily occupies vacant coordination sites, thereby preventing ruthenium hydride formation and, at higher concentrations, alkene coordination. Reducing the reaction temperature to 30 °C decreased the self-metathesis rate further, but, importantly, no isomerization could be observed even after prolonged reaction times (Table 1, entry 7). Under these reaction conditions, an optimal reaction temperature of 35 °C could be identified, leading to useful self-metathesis yields and only trace isomerization products after prolonged reaction times (Table 1, entry 8).

Table 1. Optimization of self-metathesis reaction of mannoside **M5** using catalyst **C2**.[a]



Entry	C2 (mol%)	T (°C)	Solvent	self-metathesis (%)	isomerization (%)
1	2.5	40	D_2O	5	Traces
2	2.5	50	D_2O	6	44
3	2.5	60	D_2O	5	87
4	5	40	D_2O	13	28
5	5	40	D_2O + 2.5% CD_3COOD	26/26[b]	0/6[b]
6[c]	5	40	H_2O + 5% CH_3COOH	19/22[b]	0/13[b]
7	5	30	D_2O + 2.5% CD_3COOD	16/18[b]	0/0[b]
8	5	35	D_2O + 2.5% CD_3COOD	18/27[b]	0/traces[b]

[a] Initial substrate concentration: 0.1 M. Conversions (combined *cis*/*trans*-isomers) determined by ^{1}H-NMR spectroscopy at 45-130 min. [b] Conversion at 18 h. [c] Reaction in non-deuterated solvents.

Employing the optimized reaction conditions of mannoside **M5**, the effects of the aglycone chainlength on the metathesis process were further evaluated. In principle, the catalytic performance

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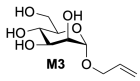
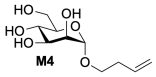
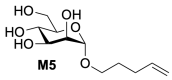
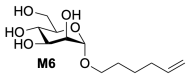
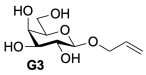
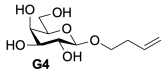
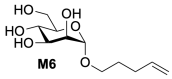
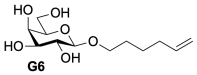
may be reduced from chelation to the ruthenium center, previously observed to play a major role in the metathesis of ammonium-functionalized alkenes.[45] To probe if such non-productive chelation indeed played a role in the reactions with unprotected carbohydrates, we synthesized a series of alkene-functionalized α-D-mannosides and β-D-galactosides containing different aglycone linker lengths (allyl, 3-butenyl, 4-pentenyl, 5-hexenyl, Table 2). In this series, the longer linker lengths were expected to contribute to the entropic factor, thereby decreasing the stability of the hypothesized chelated resting state of the catalyst.

Table 2. Self-metathesis reactions catalyzed by catalysts **C2** or **C1**.[a]

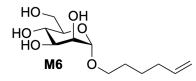
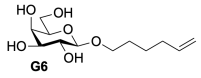
Entry	Substrate	Conversion w/ C2/C1 (%)		
		15 min	60 min	300 min
1		55/58	78/74	93/82
2		0/0	0/0	0/0
3		2/4	7/11	11/13
4		6/13	14/18	16/24
5		24/28	38/33	41/41 45/50[b]
6		0/0	0/0	0/0
7		1/2	2/4	6/5
8		6/13	14/21	16/22
9		18/25	25/31	29/33 34/47[b]

[a]Reactions performed using 5 mol% catalyst at 35 °C. Initial substrate concentration: 0.1 M in D_2O containing 2.5 vol% CD_3COOD. Conversions (combined *cis*/*trans*-isomers) determined by ^{1}H-NMR spectroscopy. [b]Conversion at 24 h.

For comparison, the self-metathesis reaction was first performed using allyl alcohol, a substrate less likely to produce non-productive chelation since it would lead to the formation of a disfavored 4-membered ring. Interestingly, the self-metathesis of allyl alcohol showed fast initiation and led to 93% conversion after only 300 min reaction time (Table 2, entry 1). As expected from the previous results, neither of the allyl glycosides **M3** or **G3** was active in the self-metathesis or isomerization reactions (Table 2, entries 2 and 6). However, higher yields were observed when the distance between the carbohydrate ring and the alkene group was increased, and the 3-butenyl glycosides **M4** and **G4** showed up to 11% conversion to the dimer (Table 2, entries 3 and 7). Further extension of the chain length to the 4-pentenyl- (**M5**/**G5**, Table 2, entries 4 and 8) and 5-hexenyl derivatives (**M6**/**G6**, Table 2, entries 5 and 9) followed the same trend, with a highest observed conversion of 41% after 300 min. Increasing the reaction time to 24 h did not result in any significantly improved dimerization efficiency, and the conversion increased up to 5%. Furthermore, both the mannosides and galactosides showed a similar trend in reactivity, with the galactosides showing only slightly lower yields.

Since the optimized procedure included the use of 2.5 vol% acetic acid, we next evaluated if the non-methylated catalyst **C1** could be used directly under the same conditions. Interestingly, this proved to be the case, and catalyst **C1** was even slightly more efficient than methylated catalyst **C2** in self-metathesis of the evaluated carbohydrates (Table 2). A likely explanation for this observation is the small increase in solubility of the catalyst as compared to catalyst **C2**, which comprises partly hydrophobic triflate anions. With catalyst **C1**, further attempts to raise the self-metathesis yields were based on observations made by the groups of Davis,[54] and Hirota,[62] where addition of a chloride salt prevented non-productive chelation/deactivation of the catalysts. In the present case, addition of magnesium chloride (100 mM) improved the self-metathesis conversions only marginally in the reactions with the functionalized carbohydrates. In contrast to the conditions without magnesium chloride, traces of product could be observed even for the allyl glycosides. However, the conversions were overall lower than observed without added salt (*cf.* supporting information, Table S1).

Table 3. Self-metathesis of 5-hexenyl glycosides **M6** and **G6** in the presence of additives.[a]

Entry	Substrate	Additive	Conversion (%)			
			15 min	60 min	300 min	24 h
1		-	28	33	41	50
2		5 mol% **C1**	48	65	76	81
3		BSA (0.01 mM)	29	36	41	50
4		BSA (0.06 mM)[b]	23	35	35	36
5		-	25	31	33	47
6		5 mol% **C1**	38	43	49	63
7		BSA (0.01 mM)	27	32	31	41
8		BSA (0.06 mM)[b]	17	26	26	28

[a] Reactions performed using 5 mol% of catalyst **C1** at 35 °C. Initial substrate concentration: 0.1 M in D_2O containing 2.5 vol% CD_3COOD. Conversions (combined *cis*/*trans*-isomers) determined by ^{1}H-NMR spectroscopy. [b] 100 wt% of BSA compared to catalyst **C1**.

The reactions of the best reacting 5-hexenyl substrates **M6** and **G6** were further studied with respect to loading and protein addition (Table 3). First, an attempt was made to improve the conversions through the addition of 5 mol% of catalyst **C1**. This increase in catalyst loading resulted in up to 81% self-metathesis of mannoside **M6**, whereas galactoside **G6** could be dimerized to an extent of 63% (Table 3, entries 2 and 6). Furthermore, to probe the compatibility of the optimized system with biologically relevant entities, such as proteins, the catalytic activity of catalyst **C1** was evaluated in the presence of bovine serum albumin (BSA). At a concentration of 0.01 mM protein, potentially acting as an external chelating moiety not participating in the catalytic cycle, the self-metathesis reaction rate was not reduced and similar conversions were observed at all time points (Table 3, entries 3 and 7). Only at the point of 0.06 mM of BSA, corresponding to 100 wt% BSA compared to catalyst **C1**, some retardation was observed. In this case, the conversion was reduced to 36% and 28% for 5-hexenyl glycosides **M6** and **G6**, respectively (Table 3, entries 4 and 8).

To expand the applicability further, the possibility to achieve cross-metathesis with the developed catalysts was explored. Similar conditions as those developed for the 5-hexenyl glycosides **M6** and **G6** were used, where allyl alcohol was added to the reaction mixtures to a final concentration of 0.1 M. Analysis of the ^{1}H-NMR spectra showed appearance of a new set of peaks corresponding to the cross-metathesis product (Figure 2). Filtration of the reaction mixture over a short path of silica and analysis by mass spectrometry confirmed the formation of the cross-metathesis products. Interestingly, after only 15 min, 35 and 36% of cross metathesis was observed for mannoside **M6** and galactoside **G6**, respectively. Simultaneously, only traces of the self-metathesis products of the glycosides could be observed. After 300 min of reaction time, the conversion to the cross-metathesis product increased by a few percent to 40 and 39%, respectively, while up to 4% of the glycoside dimers were formed. When the reaction mixture was left to stir for a total of 24 h, the conversions to the cross-metathesis products remained unchanged, whereas a significant increase in self-metathesis products could be observed with conversions up to 21 and 19% for **M6** and **G6**, respectively (Figure 2).

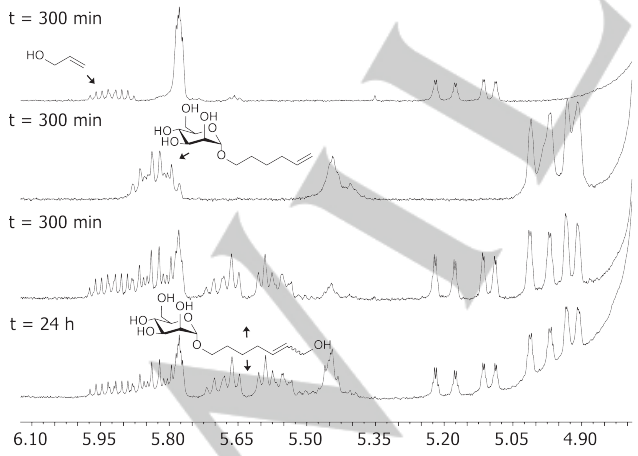


Figure 2. Alkene region of ^{1}H-NMR spectra showing the metathesis of allyl alcohol and mannoside **M6** with catalyst **C1**. Top two spectra: self-metathesis of each substrate; bottom two spectra: cross-metathesis after 300 min or 24 h reaction time.

Conclusions

In conclusion, the results show that olefin metathesis of unprotected carbohydrate structures carrying non-privileged olefin groups is feasible directly in water. Homogeneous catalytic conditions could be enabled using Hoveyda-Grubbs catalysts functionalized with morpholinium groups, conveniently synthesized in few steps. Both self-metathesis and cross-metathesis could be achieved using the catalysts, and the addition of small quantities of acetic acid to the solutions was found to deter alkene isomerization and increase the formation of the metathesis products. This simultaneously allowed for direct use of the non-methylated catalyst **C1**, thereby further shortening the synthetic route to this catalyst. The catalytic activity of catalyst **C1** was furthermore maintained in the presence of large amounts of albumin, demonstrating the stability and high compatibility of the catalyst under challenging conditions. Overall, the results of this study demonstrate a broadened substrate scope of aqueous olefin metathesis, increasing the capability of forming carbon-carbon bonds under catalytic conditions in demanding aqueous environments. The results furthermore indicate the potential of using these catalysts for biological applications, such as in drug discovery and protein derivatization.

Experimental Section

Experimental Details.

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Keywords: olefin metathesis • carbohydrates • homogeneous catalysis • aqueous media • synthetic methods

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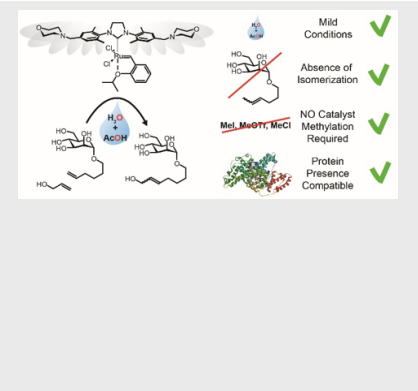
Water-soluble Hoveyda-Grubbs catalysts were synthesized and applied to metathesis of unprotected alkene-functionalized glycopyranosides under mildly acidic aqueous conditions. Through minimization of non-productive chelation and isomerization, both self-metathesis and cross-metathesis could be achieved. The catalytic activity was furthermore retained in the presence of serum albumin.



*Brian J.J. Timmer and Olof Ramström**

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Acid-Assisted Direct Olefin Metathesis of Unprotected Carbohydrates in Water