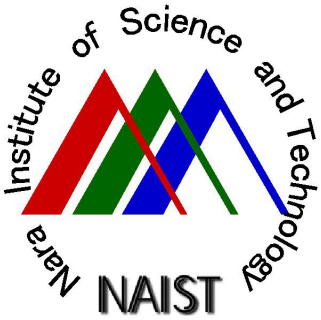
Precise Synthesis of Carbohydrate Polymers by Transition Metal Catalyzed Living Ring-Opening Metathesis Polymerization

（遷移金属錯体触媒を用いるリビング開環メタセシス重合による糖鎖置換ポリマーの精密合成）



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December 2004

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Chapter 1

General Introduction

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1-1. Synthesis and Function of Carbohydrate Polymers

Carbohydrates occurring in cell membranes play an important role in cellular recognition and signaling transduction such as multiplication, adhesion, and growth. The binding epitope density and spatial arrangement of the carbohydrates effect carbohydrate-protein interactions, because an unexpected, both specific and strong affinity can be observed with multivalent ligands that can be explained as their clustering and binding into multivalent arrays which lead to a greater affinity and specificity, although the affinities with monovalent interactions are extremely weak.[1-3] In addition, numerous cellular recognition processes depend on protein-carbohydrate interactions, and these lectin-ligand attachments are critical in fertilization, cell signaling, pathogen identification, and the inflammatory response.[4,5]

Recently, many researches have been done to create intelligent materials with highly specified functions in the field of polymer synthetic chemistry. In order to create these materials, we need to clarify the correlation between the primary structure and the function of the resultant polymer. Recently, many researchers are conducting studies concerning the synthesis and function of a variety of carbohydrate polymers.[6] The carbohydrate polymers, are classified into two types; (i) principal-chain carbohydrate polymers, and (ii) side-chain carbohydrate polymers (Figure 1-1). In particular, compared to principal-chain carbohydrate polymers (e.g. hyaluronic acid, and heparin), side-chain carbohydrate polymers (e.g. lactose-substitute polystyrene[7]) should be more suited for the precise design of chain length of principal- or side-chain using spacer. This is because, that the control both the distance and spatial arrangement of carbohydrates in the case of side-chain carbohydrate polymers. As a result of precise arrangement of the binding epitope density of carbohydrate polymer, we can thus expect to increase the recognition of carbohydrate polymers, in comparison to low-molecular weight scaffolds bearing carbohydrates. Therefore,

we focused on the preparation of side-chain carbohydrate polymers.

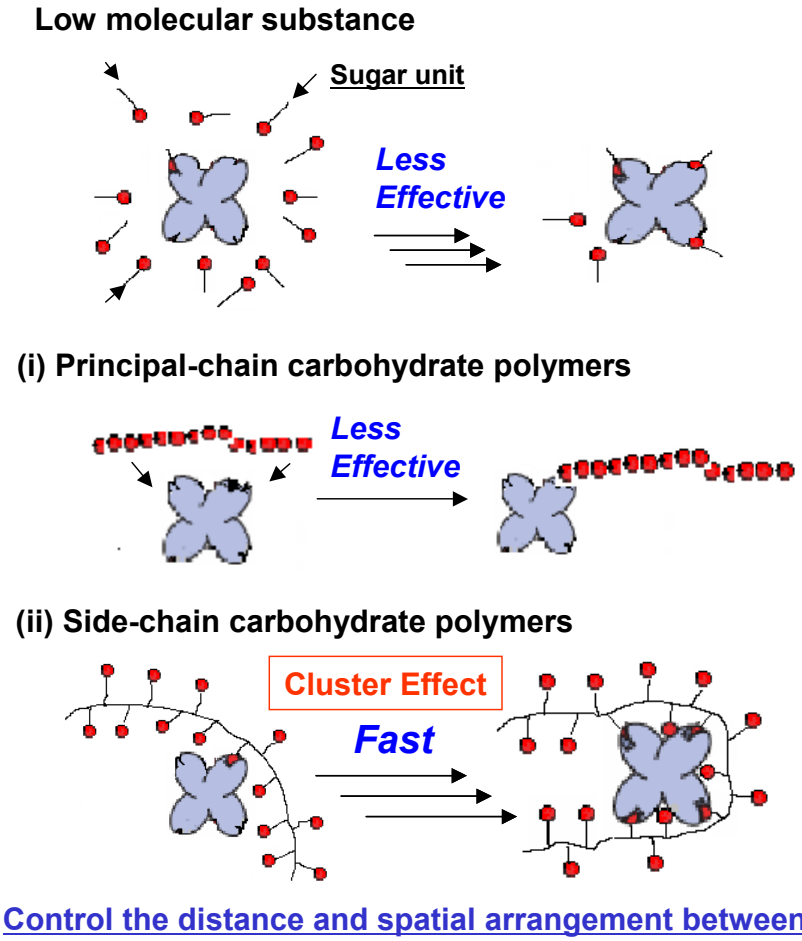


Figure 1-1. Schematic drawing for multivalent ligand-promoted clustering of Lectin. (Blue shapes represent tetrameric Concanavalin A)

1-2. Previous Example for Synthesis of Carbohydrate-Substituted Polymers (Neobiopolymers)

Many efforts have been described for the synthesis of polymers containing carbohydrate residues using radical, cationic/anionic and coordination polymerization.[8,9] In the beginning of the 1990s, Whitesides reported that polyacrylamides bearing pendant α-sialoside groups strongly inhibited agglutination of erythrocytes of the influenza virus.[10] Since then, many researchers have developed carbohydrate functionalized polymers to investigate

the function of the side-chain carbohydrate on account of this work. For example, Kiessling reported that carbohydrate polymers prepared by aqueous ROMP, acted as a potent inhibitor of concanavalin A (Con A)-induced cell agglutination, although both description of the molecular weight and molecular weight distribution of the carbohydrate ROMP polymers were not described.[11]

Recently, Kiessling also reported that carbohydrate ROMP polymers acted as better potent inhibitors of Con A, than other carbohydrate polymers of varied principal-chain type (vinylpolymer, dendrimer, and low-molecular substance).[12] Therefore, the synthesis of carbohydrate polymers by the ROMP technique has attracted considerable attention,[11-22] especially since Kiessling et al,[12] demonstrated that relatively linear polymers prepared by ROMP possessed structural properties that favor clustering. However, reports concerning the precise control of molecular weight, chain length, as well as the preparation of block copolymers have been limited.[18,19,21-22] Examples of the precise synthesis methods including radical,[7,23] cationic/anionic,[24] ring-opening polymerization (ROP),[25,26] and coordination polymerization[27] have also been limited so far.

1-3. Ring-Opening Metathesis Polymerization (ROMP)

Many studies have been made concerning ROMP, especially the polymerization of norbornene and numerous derivatives using transition-metal-catalysts (Ti, V, Mo, W, and Ru etc).[28-31] The mechanism of the ROMP reaction involves an alkylidene initiators breaking and reforming olefin double bonds with simultaneous opening of unsaturated cyclic of monomers (Figure 1-2). Initiation takes place by the cycloaddition of metal-carbene complexes to the carbon-carbon double bond of the cyclic olefin, affording the formation of an intermediate called metallacyclobutane. This undergoes a retrocycloaddition to form the initiating species propagation of a second monomer

unit by the first insertion product proceed via the same metallacyclobutane. The reaction proceeds with this manner until all monomer is consumed.

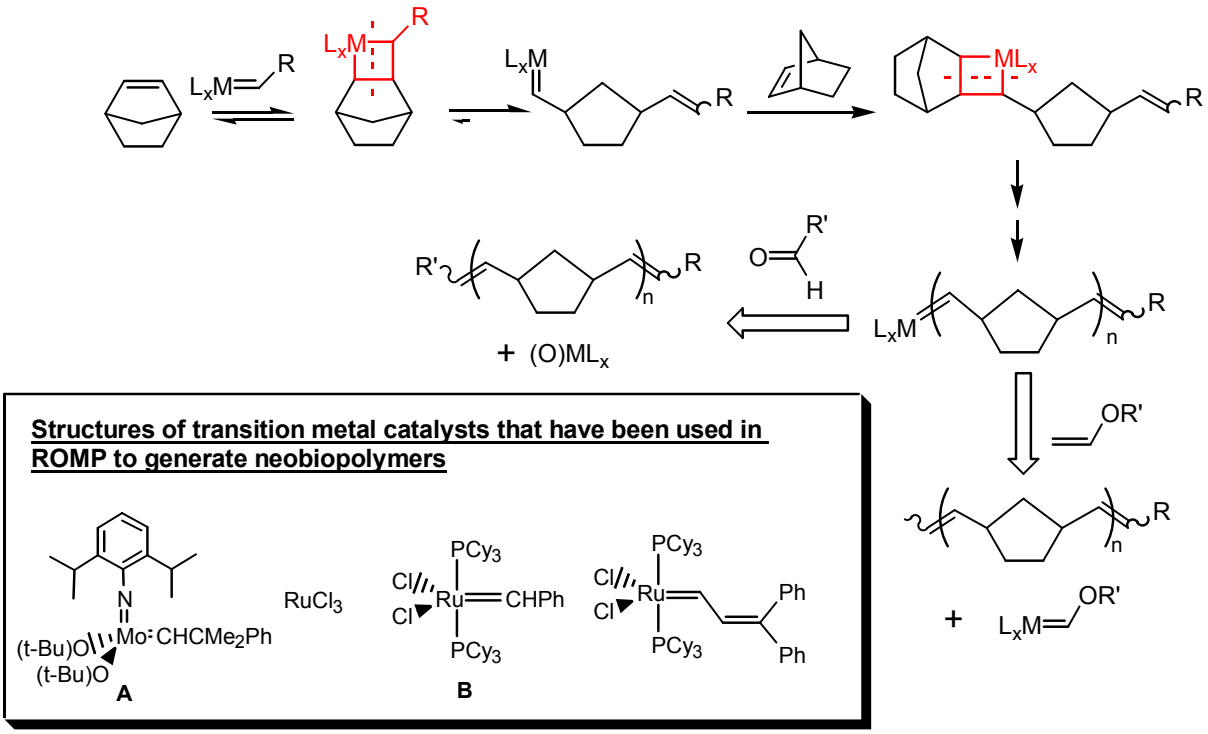


Figure 1-2. The mechanism of the ROMP reaction using transition-metal-catalysts.

As mentioned above, the design of synthetic biopolymers must be considered as the target specific molecules with conformational or functional properties. In fact, many interesting efforts have thus resulted in the preparation of polymers with biological functional groups by ROMP[8,9] (Figure 1-3). These examples include carbohydrates,[11-22] peptides,[32-33] nucleic acid bases[34] and even penicillin[35] functionality incorporated onto the polymer backbone. Recently, the ROMP polymers have found applications in industry and current research is focused on elegant syntheses with ROMP as the key step for preparing materials for diverse applications.

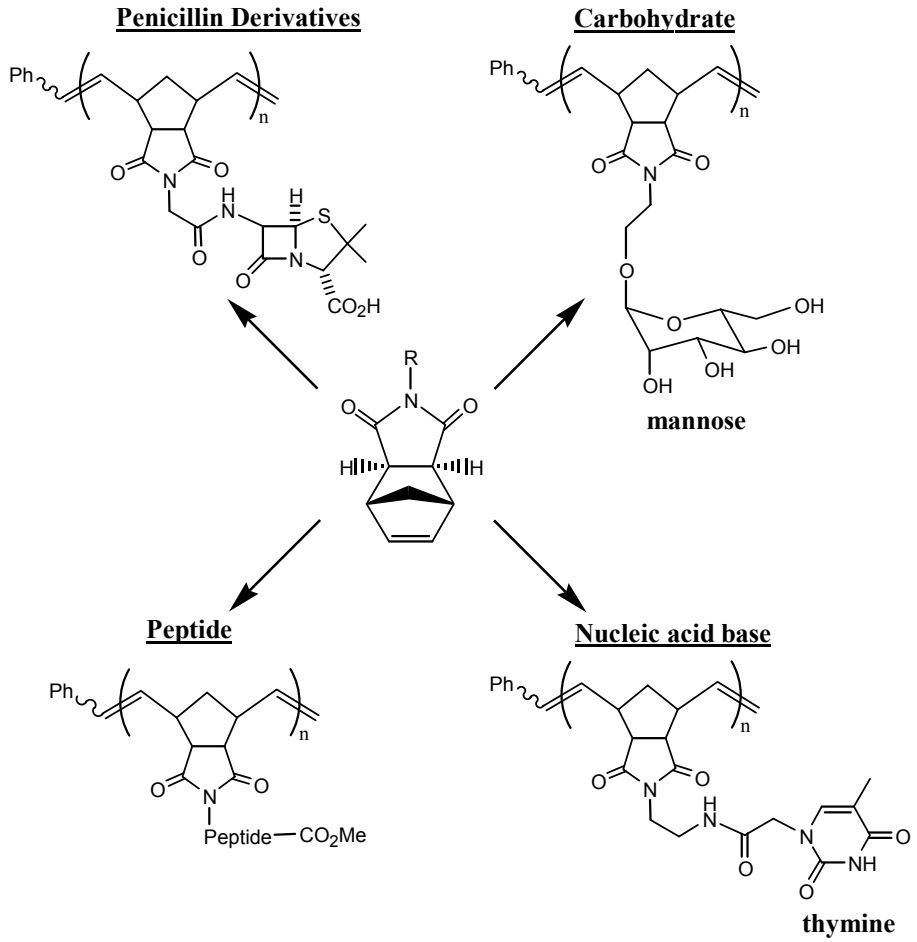


Figure 1-3. Biologically active polymers synthesized via ROMP.

1-4. History of Carbohydrate-Substituted Polymers Generated by ROMP

Many reports have been known for the synthesis of polymers containing carbohydrate residues using ROMP. As the first report of biologically active ROMP polymers, Kiessling reported the synthesis and biological evaluation of carbohydrate ROMP polymers.[11] The polymerization of saccharide-substituted monomers was carried out using $RuCl_3$ as the initiator. However, these reports did not describe molecular weight distribution of the resultant carbohydrate ROMP polymers. In contrast, Schrock and Nomura reported that the living ROMP technique using a Schrock-type molybdenum-alkylidene initiator, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}^{i}Pr_2C_6H_3)(O^{t}Bu)_2$, is effective for the preparation of

homopolymers and multi-block copolymers containing acetal-protected monosaccharide residues such as galactose, ribose, and mannose.[18] Fraser and Grubbs investigated the ROMP of glucose-substituted norbornenes using ruthenium-carbene initiators, $(Cy_3P)_2RuCl_2(CHPh)$ and $(Ph_3P)_2RuCl_2(CHPh)$.[19] However, this report mainly focused on the effect of the sugar protecting group based on this monomer by ROMP. More recently, Chaikof and coworkers reported the synthesis of ROMP polymers containing hyaluronan (HA)-derived disaccharide using the 2nd generation ruthenium-carbene initiators, $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ ($IMesH_2$ = 1,3-dimesityl-4,5-dihydromidazol-2-ylidene).[21] As mentioned above, a variety of carbohydrate ROMP polymers were synthesized using transition metal catalysts (Chart 1-1, Figure 1-4) which were of interest in the fields of carbohydrate biology and chemistry.[8, 9, 11-22, 36-48] However, most of all reports by transition metal catalyzed polymerization did not describe the molecular weight and molecular weight distribution of the carbohydrate ROMP polymers.[18, 19, 21, 22]

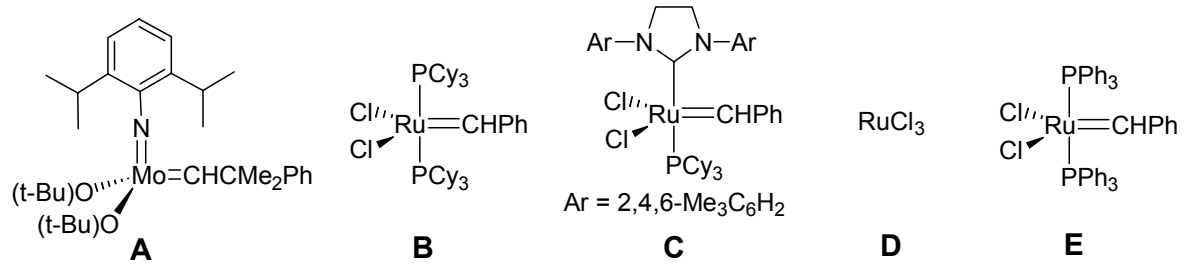


Chart 1-1. Molybdenum (**A**) and ruthenium (**B, C, D,** and **E**) initiators.

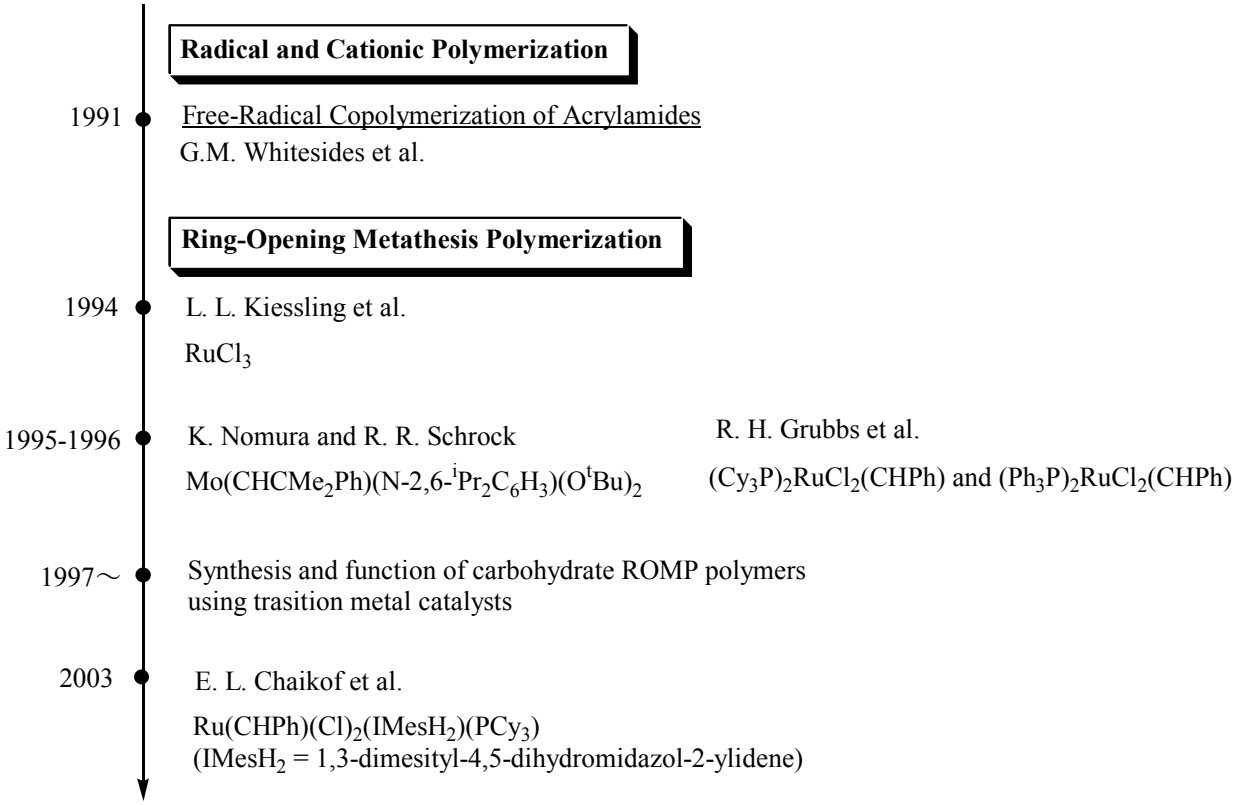


Figure 1-4. Time line of milestones in the development of carbohydrate ROMP polymers.

1-5. Functional Group Tolerance of Early and Late Transition Metal Olefin Metathesis Catalysts

For these three decades, Schrock, Grubbs and many other researchers have studied the development (design, synthesis, and function) of transition metal olefin metathesis catalysts.[49] The unique characteristics of using the ruthenium-based catalysts was proposed in 2001 (Figure 1-5) by Trnka and Grubbs, and they summarized the functional group tolerance of early and late transition metal olefin metathesis catalysts and investigated the deactivation of catalysts by functional groups in the substrate or solvent, including oxygen and water. As shown in Figure 1-5, molybdenum, titanium, and tungsten catalysts are highly

reactive toward cyclic olefins, although they also react with aldehydes, alcohols, water, and acids. In comparison, ruthenium catalysts show highest reactivity toward carbon-carbon double bonds than acids, aldehydes, and amides functionalities etc. Therefore, in terms of usefulness (availability, ease of synthesis, and functional group tolerance), ruthenium catalysts should have an advantage over molybdenum catalysts. In fact, Kiessling succeeded in the synthesis of carbohydrate ROMP polymers using ruthenium catalysts under aqueous conditions (without unprotected hydroxyl groups of the carbohydrate).[11] However, almost all reports by ruthenium catalysts did not described molecular weight and molecular weight distribution of carbohydrate ROMP polymers.[19, 21]

Titanium	**Tungsten**	**Molybdenum**	**Ruthenium**
Acids	Acids	Acids	**Olefins**
Alcohols, Water	Alcohols, Water	Alcohols, Water	Acids
Aldehydes	Aldehydes	Aldehydes	Alcohols, Water
Ketones	Ketones	**Olefins**	Aldehydes
Esters, Amides	**Olefins**	Ketones	Ketones
Olefins	Esters, Amides	Esters, Amides	Esters, Amides

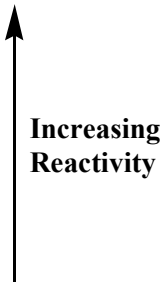


Figure 1-5. Functional group tolerance of early and late transition metal olefin metathesis catalysts.

1-6. Precise Synthesis of Carbohydrate ROMP Polymers

In previous reports, Schrock has proven that ROMP with the molybdenum initiators takes place in a living fashion.[50] With respect to the synthesis of carbohydrate ROMP polymers, Schrock and Nomura reported that the living ROMP technique, using a molybdenum initiator, is effective for the preparation of

homopolymers and multi-block copolymers with uniform composition.[18] In contrast, Grubbs reported that ROMP with ruthenium initiator took place in a living fashion depending on the specific substrate.[51] It is believed that initiation efficiency is dependent on substrates. Due to the easily handled ruthenium catalysts, (high functional group tolerance, ever in water without unprotected carbohydrate hydroxyl groups), carbohydrate ROMP polymers could be synthesized easily. However, this polymerization did not indicate a living polymerization with quantitative initiation.

1-7. Purpose on this work

In this thesis, the development of new synthetic methodology using transition metal catalysts have been focused, resulting in the preparation of carbohydrate ROMP polymers with precise control of primary structure (molecular weight, composition) of carbohydrate ROMP polymers.

In a previous report, Schrock and Nomura proved that ROMP with molybdenum initiators took place in a living fashion.[18] However, molecular weight and molecular weight distributions of the resultant polymers were dependent on the solvent and the polymerization time. For this reason, it was assumed the cleavage of the acetal group protected for sugar residue. In order to resolve this problem, we tried to polymerize norbornenes containing acetyl-protected carbohydrate residues under controlled conditions, (highly purified monomers, anhydrous solvents, and a nitrogen atmosphere).[22]

In previous reports using ruthenium initiators, Kiessling and co-workers did not indicate that the polymerization took place in a living fashion, and the preparation of multi-block copolymers have not been successful. For this reason, we believed that deactivation of the ruthenium initiators occurred (for example; reaction with hydroxyl group of carbohydrate, water, and oxygen). A new

strategy to resolve this problem, was to try the ROMP of norbornenes containing acetyl-protected carbohydrates under the same conditions with molybdenum initiators. In addition, ruthenium catalyst **C** is known for indication of high reactivity with cyclic olefins. We thus explored the possibility to synthesize carbohydrate ROMP polymers using ruthenium catalyst **C**.

This thesis consists of two chapters with the theme of living ROMP of norbornenes containing acetyl-protected carbohydrates using transition metal catalysts as mentioned above. One is the synthesis of carbohydrate polymers using ruthenium catalysts and the other is kinetic studies, the effect of catalysts and solvents.

In chapter 2, the ROMP of norbornenes containing acetyl-protected carbohydrates using ruthenium catalysts was conducted at various monomer/Ru molar ratios and the molecular weight and M_n, M_w/M_n values of resulting carbohydrates polymers were studied by GPC. Preparation of multi-block ROMP copolymers containing sugars conducted at various monomer/Ru molar ratios.

In chapter 3, since first order relationships between the propagation rate and the monomer concentration were observed in all polymerization runs, we thus estimated the k values (rate constants) for polymerization of **1** and **2** using molybdenum and ruthenium initiators in various solvents at 25 ºC. We also wish to present our explored results to compare the initiator performances for ROMP using well-defined molybdenum and ruthenium initiators under the same conditions.

1-8. References

1. Mann, D. A.; Kiessling L. L. In *Glycochemistry*; Wang, P. G. and Bertozzi, C. R., Eds.; Marcel Dekker Inc.: NewYork, 2001; pp 221-275.
2. Lee, Y.; Lee, R. *Acc. Chem. Res.* **1995**, *28*, 321-327.
3. Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555-578.
4. Drickamer, K.; Taylor, M. E. *Ann. Rev. Cell Biol.* **1993**, *9*, 237-264.
5. Varki, A. *Glycobiology* **1993**, *3*, 97-130.
6. Wang, Q.; Dordick, J. S.; Linhardt, R. J. *Chem. Mater.* **2002**, *14*, 3232-3244.
7. Kobayashi, K.; Tsuchida, A.; Usui, T.; Akaike, T. *Macromolecules* **1997**, *30*, 2016-2020.
8. Kiessling, L. L.; Strong, L. E. In *Alkene Metathesis in Organic Synthesis*; Fürstner, A. Ed.; Springer-Verlag: Berlin, 1998; pp 199-231.
9. Kiessling, L. L.; Owen, R. M. In *Handbook of Metathesis*: Grubbs R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol 3, pp 180-225.
10. Spaltenstein, A.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 686-687.
11. Mortell, K. H.; Gingas, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **1994**, *116*, 12053-12054.
12. Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922-14933.
13. Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297-2298.
14. Manning, D. D.; Hu, X.; Beck, P.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 3161-3162.
15. Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931-9932.
16. Gordon, E. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30-31.
17. Cairo, C. W.; Gestwicki, J. E.; Kanai, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 1615-1619.

18. Nomura, K.; Schrock, R. R. *Macromolecules* **1996**, *29*, 540-545.
19. Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248-7255.
20. Meier, S.; Reisinger, H.; Haag, R.; Mecking, S.; Müllhaupt, R.; Stelzer, F. *Chem. Commun.* **2001**, 855-856.
21. Iyer, S.; Rele, S.; Grasa, G.; Nolan, S.; Chaikof, E. L. *Chem. Commun.* **2003**, 1518-1519.
22. Nomura, K.; Sakai, I.; Imanishi, Y.; Fujiki, M.; Miyamoto, Y. *Macromol. Rapid Commun.* **2004**, *25*, 571-576.
23. Ohno, K.; Tsujii, Y.; Miyamoto, T.; Fukuda, T.; Goto, M.; Kobayashi, K.; Akaike, T. *Macromolecules* **1998**, *31*, 1064-1069.
24. Yamada, K.; Minoda, M.; Miyamoto, T. *Macromolecules* **1999**, *32*, 3553-3558.
25. Aoi, K.; Tsutsumiuchi, K.; Okada, M. *Macromolecules* **1994**, *27*, 875-877.
26. Tsutsumiuchi, K.; Aoi, K.; Okada, M. *Macromolecules* **1997**, *30*, 4013-4017.
27. Wang, J.; Tomita, I. *Macromolecules* **2001**, *34*, 4294-4295.
28. Black, G.; Maher, D.; Risse, W. In *Handbook of Metathesis*; Grubbs, R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol 3, pp 2-71.
29. Natta, G.; Asta, G. D.; Motroni, G. *J. Polymer. Sci., Part B.* **1964**, *2*, 349-351.
30. Grubbs, R. H. In *Handbook of Metathesis*; Grubbs, R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol 1, pp xxi-xxv.
31. Banks, R. L.; Bailey, G. C. *Ind. Eng. Chem. Prod. Res. Dev.* **1964**, *3*, 170.
32. Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules* **2000**, *33*, 6239-6248.
33. Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 1275-1279.
34. Gibson, V. C.; Marshall, E. L.; North, M.; Robson, D. A.; Williams, P. J. *Chem. Commun.* **1997**, 1095-1096.
35. Biagini, S. C. G.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; North, M. *Chem. Commun.* **1997**, 1097-1098.

36. Schuster, M. C.; Mortell, K. H.; Hegeman, A. D.; Kiessling, L. L. *J. Mol. Catal. A: Chem*. **1997**, *116*, 209-216.

37. Pohl, N. L.; Kiessling, L. L. *Synthesis* **1999**, No. SI, 1515–1519.

38. Sanders, W. J.; Gordon, E. J.; Dwir, O.; Beck, P. J.; Alon, R.; Kiessling, L. L. *J. Biol. Chem*. **1999**, *274*, 5271-5278.

39. Strong, L. E.; Kiessling, L. L. *J. Am. Chem. Soc*. **1999**, *121*, 6193-6196.

40. Yang, Z. Q.; Puffer, E. B.; Pontrello, J. K.; Kiessling, L. L. *Carbohyd. Res*. **2002**, *337*, 1605-1613.

41. Gordon, E. J.; Gestwicki, J. E.; Strong, L. E.; Kiessling, L. L. *Chem. Biol*. **2000**, *9*, 9-16.

42. Owen, R. M.; Gestwicki, J. E.; Young, T.; Kiessling, L. L. *Org. Lett*. **2002**, *4*, 2293-2296.

43. Gestwicki, J. E.; Strong, L. E.; Kiessling, L. L. *Angew. Chem., Int. Ed*. **2000**, *39*, 4567-4570.

44. Gestwicki, J. E.; Cairo, C. W.; Mann, D. A.; Owen, R. M.; Kiessling, L. L. *Anal. Biochem*. **2002**, *305*, 149-155.

45. Gestwicki, J. E.; Strong, L. E.; Kiessling, L. L. *Chem. Biol*. **2000**, *0*, 1-9.

46. Gestwicki, J. E.; Kiessling, L. L. *Nature* **2002**, *415*, 81-84.

47. Lamanna, A. C.; Gestwicki, J. E.; Strong, L. E.; Borchardt, S. L.; Owen, R. M.; Kiessling L. L. *J. Bacteriol*. **2002**, *184*, 4981-4987.

48. Gestwicki, J. E.; Strong, L. E.; Borchardt, S. L.; Cairo, C. W.; Schnoes, A. M.; Kiessling, L. L. *Bioorg. Med. Chem*. **2001**, *9*, 2387-2393.

49. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18-29.

50. Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc*. **1990**, *112*, 8378-8387.

51. Wu, Z.; Benedicto, A. D.; Grubbs, R. H. *Macromolecule*s **1993**, *26*, 4975-4977.

Chapter 2

Synthesis of Homopolymers and Multiblock Copolymers by Living Ring-Opening Metathesis Polymerization (ROMP) of Norbornenes Containing Acetyl-Protected Carbohydrates Using Well-Defined Ruthenium Initiators

Contents

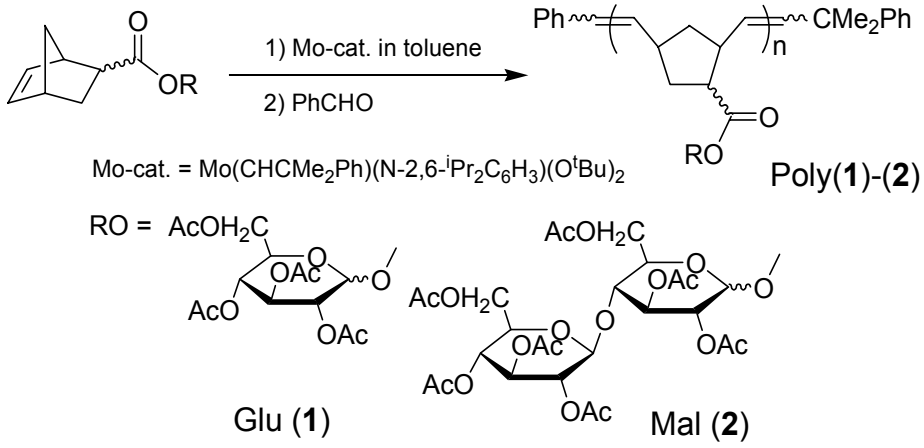
2-1. Introduction

Carbohydrate functionalized polymers have attracted considerable attention, because an unexpected both specific and strong affinity can be observed with multivalent ligands that can be explained as clustering of binding into multivalent arrays which lead to a greater affinity and specificity although the affinities with monovalent interactions were extremely weak.[1,2] In addition numerous cellular recognition processes depend on protein-carbohydrate interactions, and these lectin-ligand attachments are critical in fertilization, cell signaling, pathogen identification, and the inflammatory response.[3,4]

Many efforts have been known for the synthesis of polymers containing carbohydrate residues using radical, cationic/anionic and coordination polymerization.[5,6] In particular, their synthesis by ROMP has attracted considerable attention,[7-18] as a result of reports by Kiessling et al.[13] demonstrating that relatively linear polymers prepared by ROMP possessed structural properties that favor clustering. On the other hand, however, reports concerning the precise control of molecular weight, chain length, as well as the preparation of block copolymers have been limited so far.[14,15,17-19]

It has been reported that living ROMP using a Schrock-type molybdenum-alkylidene initiator, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}^{i}Pr_2C_6H_3)(O^{t}Bu)_2$ (**A**), is an effective method of preparing homopolymers and multi-block copolymers containing acetal-protected monosaccharide residues such as galactose, ribose, and mannose.[14] More recently, we reported in a preliminary communication that this technique was also effective to prepare homopolymers and diblock copolymers that contain acetyl-protected glucose [monosaccharide; i.e., 2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate (**1**)] or maltose [disaccharide; i.e., 2,3,6,2',3',4',6'-hepta-*O*acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate (**2**)] residues (Scheme 2-1) and that these polymerizations took place not only in a living fashion (M_w/M_n = <1.2) but also with almost quantitative

initiation.[18,20] Although examples for the synthesis of bioactive polymers via ROMP using ruthenium initiators[21-25] have been widely reported,[5-13,15,17,29-31] as far as we know, examples comparing the initiator performances under the same conditions (especially for ROMP) have been limited.[25-27] Moreover, descriptions concerning the molecular weight distributions for resultant carbohydrate based ROMP polymers prepared by ruthenium initiators have not been reported, except in publications by Fraser and Grubbs[15] and Chaikof et al.[17] A comparison of these initiators under the same conditions should be important for the design of the better initiators as well as for preparing desired polymers in a controlled fashion. In this chapter, we thus wish to introduce the synthesis of homopolymers and block copolymers containing carbohydrates by living ROMP using the ruthenium initiators, $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**; Cy = cyclohexyl) and $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**; $IMesH_2$ = 1,3-dimesityl-4,5-dihydromidazol-2-ylidene) (Scheme 2-1 and Chart 2-1).



Scheme 2-1

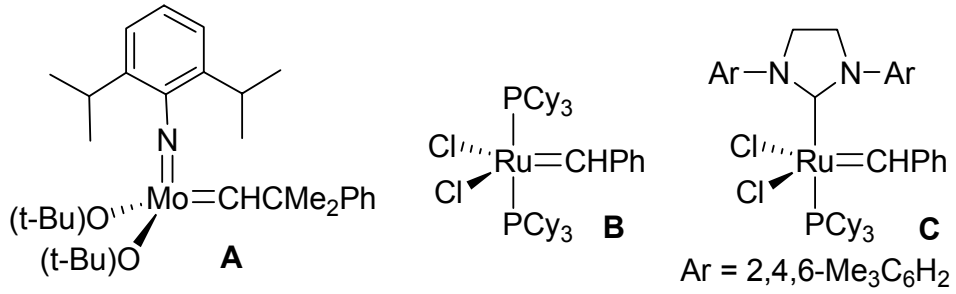


Chart 2-1. Molybdenum (**A**) and ruthenium (**B** and **C**) initiators.

2-2. Experimental

Materials

General procedure

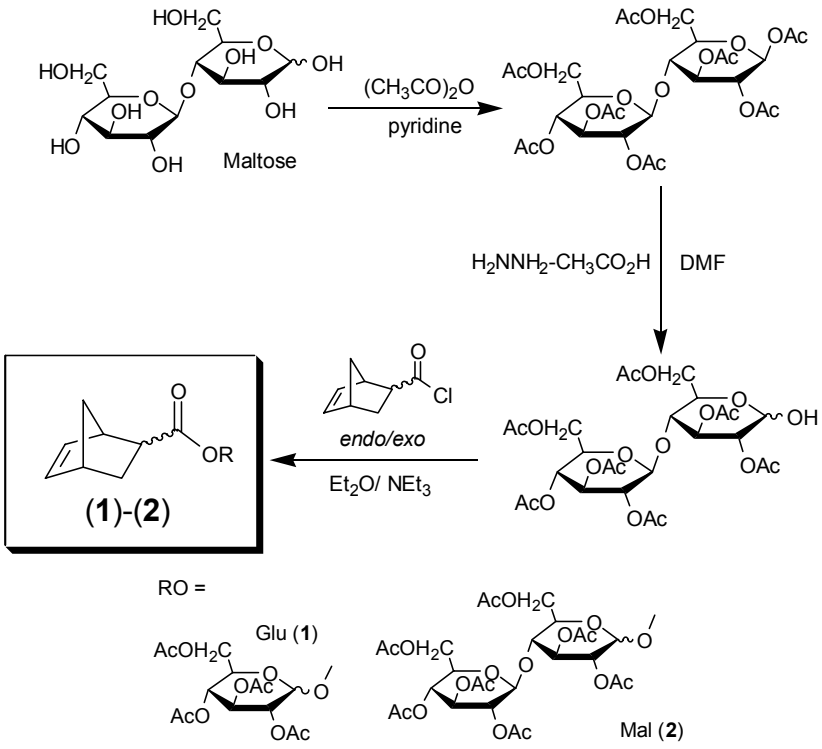
All experiments were carried out under a nitrogen atmosphere in a Vacuum Atmospheres drybox or using standard Schlenk techniques. All chemicals used were of reagent grade and were purified by the standard purification procedures. Polymerization grade toluene was distilled from sodium and benzophenone, stored over sodium/potassium alloy in a drybox, and was then passed through an alumina short column prior to use. Anhydrous grade of diethyl ether, CH_2Cl_2, THF, and *n*-hexane (Kanto Kagaku Co. Ltd) were transferred into a bottle containing molecular sieves (mixture of 3A, 4A 1/16, and 13X) in the drybox. Commercially available $CDCl_3$ and toluene-d_8 were also transferred into a bottle containing molecular sieves in the drybox, and were passed through an alumina short column prior to use. $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}{}^{i}Pr_2C_6H_4)(O^{t}Bu)_2$ (**A**),[32-33] and 5-norbornene carboxylic acid chloride[34,35] (*endo*/*exo* = 87/13) were prepared according to the literature. $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**) and $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**) shown in Chart 2-1 were purchased from Strem Chemicals, Inc., and were used in the drybox without further purification.

All ^{1}H- and ^{13}C-NMR spectra were recorded on a *JEOL* JNM-LA400 spectrometer (^{1}H, 399.65 MHz; ^{13}C, 100.40 MHz), and were obtained in the solvent indicated at 25 ºC, with the chemical shifts given in ppm and referenced to $SiMe_4$. HPLC grade THF was used for GPC and was degassed prior to use. GPC were performed at 40 ºC on a Shimazu SCL-10A using a RID-10A detector (Shimazu Co. Ltd.) in THF (containing 0.03 wt% 2,6-di-*tert*-butyl-*p*-cresol, flow rate 1.0 mL/min). GPC columns (ShimPAC GPC-806, 804 and 802, 30 cm x 8.0 mmϕ) were calibrated vs polystyrene standard samples. FAB-MS spectra were taken by using JEOL JMS-700 Mstation (JEOL Co.) with 3-nitrobenzyl alcohol (NBA) matrix. Elemental analyses were performed by using PE2400II Series (Perkin Elmer Co.).

Monomer synthesis

2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate (2).

Monomer **2** was prepared according to Scheme 2-2 from D-maltose as the starting compound, and maltose peracetate and 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltose were prepared according to the established procedure.[36-38] Treatment of maltose with acetic anhydride in pyridine afforded maltose octaacetate, which was treated with hydrazine acetate in DMF to afford 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltose.



Scheme 2-2. Synthesis of ester-type norbornene derivatives containing glucose (**1**), and maltose (**2**).

2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltose: ^{1}H ($CDCl_3$): δ 5.54 and 5.25 (t, 1H), 5.39 and 5.35 (d, 1H), 5.28-5.33 (2H), 5.04 and 5.00 (t, 1H), 4.80-4.84 (1H), 4.68-4.74 (1H), 4.44-4.47 (1H), 4.20 and 4.19 (1H), 4.14-4.24 (2H), 4.03 and 3.98 (1H), 3.90-3.98 (2H), 3.76 or 2.79 (br., 1H, OH), 2.05 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.93 (s, 3H), 1.92 (s, 3H), 1.19 (s, 3H). ^{13}C ($CDCl_3$): δ 170.5, 170.5, 170.4, 170.3, 170.2, 170.1, 170.0, 169.8, 169.8, 169.3, 169.3 ($CH_3\underline{C}O$-), 95.3, 95.2, 95.2, 95.1, 89.6, 89.4, 74.9, 74.8, 73.2, 73.3, 72.5, 72.1, 72.0, 71.9, 71.5, 71.4, 69.8, 69.7, 69.0, 68.2, 68.1, 67.8, 67.7, 67.2, 62.6, 61.2, 20.2-20.7 ($\underline{C}H_3CO$-).

A solution of 2-norbornene-5-carboxylic acid chloride (0.28 g, 1.79 mmol) in THF (5 mL) was added dropwise over a period of 30 min into a THF solution (40 mL) containing of 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltose (1.03 g, 1.62

mmol), triethylamine (0.19 g, 1.88 mmol) at -30 ºC. The mixture was warmed slowly to room temperature, and the solution stirred for 8 h. The white precipitate was filtered off and the filter cake was washed with THF, and the combined filtrate and the wash were placed in a rotary evaporator to remove THF *in vacuo*. The resultant chunk was dissolved with a minimum amount of THF. The dropwise addition of the THF solution into a vigorously stirred ice water gave white granular chunks, which were dried *in vacuo* overnight. The resultant solid was placed in the drybox, dissolved with a minimum amount of ether, and then quickly passed through an alumina pad. The ether solution was evaporated *in vacuo* to give a granular product. The crystallization from chilled (-30 ºC) dichloromethane/hexane gave white microcrystals (0.94 g, 1.24 mmol, Yield 76.5 %). Pure monomer **2** for ROMP was prepared by the repeated recrystallization in the drybox (yield 43.0 %). 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate (**2**). ^{1}H ($CDCl_3$): resonances at 6.11, 6.06, 6.00, 5.83 and 5.64 (dd or m, 2H) are due to the olefinic proton of norbornene (*endo/exo*-), resonances at δ 5.31 (d, 1H), 5.23 and 5.24 (1H), 5.57-5.71 and 5.17-5.29 (m, 2H), 4.86-4.98 (m, 2H), 4.76 (m, 1H), 4.34 and 4.37 (m, 1H), 4.11-4.17 (m, 2H), 3.91-3.98 (m, 2H), 3.84 and 3.87 (1H), 3.73 (m, 1H) are due to protons of the maltose residue (total 14H), resonances at 3.28, 3.23, 3.12, 3.03, 2.93, 2.89 (m), 2.83, 2.15 (m), 1.80 (m), 1.24-1.34, 1.17 are due to the non-olefinic norbornene protons (total 7H, *endo*/*exo* mixture), 1.89-2.00 (m, 21H, $C\underline{H}_3CO$). ^{13}C ($CDCl_3$): δ 172.4, 172.3 (C=O), 170.3, 170.3, 170.2, 170.1, 169.8, 169.6, 169.3, 169.2 ($CH_3C\underline{O}$), 138.4, 138.1, 137.1, 132.2, 132.1, 131.5, 131.1 (olefinic), 95.5, 90.9, 75.0, 72.7, 72.3, 72.0, 70.4, 69.9, 69.6, 69.1, 68.4, 67.8, 62.3, 61.3 (due to the maltose residue), 49.5, 49.2, 46.2, 45.6, 45.5, 43.1, 43.0, 42.4, 29.0, 28.4 (five-membered ring), 20.4-20.7 ($\underline{C}H_3CO$-). Anal. Calcd for $C_{34}H_{44}O_{19}$: C, 53.97; H, 5.86. Found: C, 53.72; H, 5.80. FAB-MS Calcd for $C_{34}H_{44}O_{19}$ $[M+Na]^+$ 779.2375, Found 779.2385.

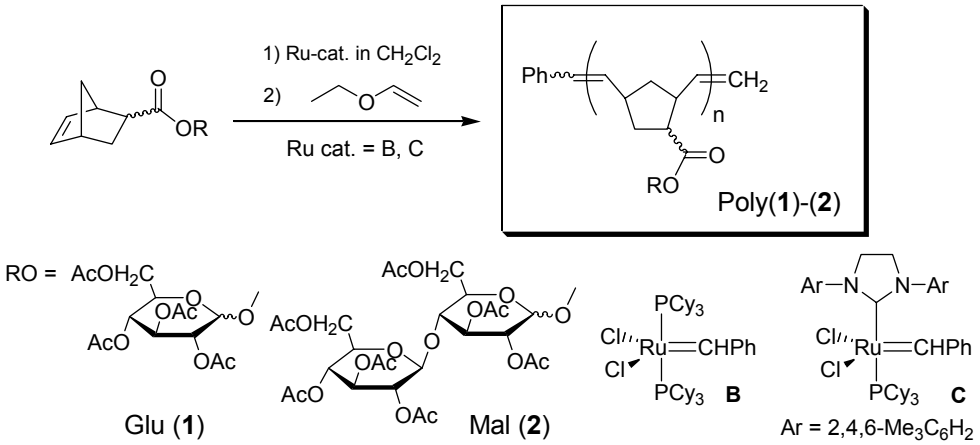
2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate (1).

Basic synthetic procedure for **1** was the same as that for **2**, except that glucose was used in stead of maltose. Yield 70.6 % (from 2,3,4,6-tetra-*O*-acetyl-glucose). 2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylayte (**1**). ^{1}H NMR ($CDCl_3$): resonances at δ 6.14, 6.08, 6.03, 5.87 and 5.66 (m, 2H) are due to the olefinic proton of norbornene (*endo/exo*-), resonances at 5.56 (t) and 5.35-5.45 (m, 1H), 4.98-5.20 (m, 3H), 4.20-4.24 (m, 1H), 4.00 and 4.03 (1H), 3.75 (m, 1H) are due to protons of the glucose residue (total 7H), resonances at 3.16, 3.07, 3.00, 2.93, 2.90 (m), 2.84, 2.18 (m), 1.84 (m), 1.24-1.40, 1.18 are due to the non-olefinic norbornene protons (total 7H, *endo*/*exo* mixture), 1.93-2.00 (m, 12H, $C\underline{H}_3CO$). ^{13}C NMR ($CDCl_3$): δ 172.6, 172.5 ($\underline{C}$=O), 170.4, 169.9, 169.2, 169.0, 168.9 ($CH_3\underline{C}O$), 138.5, 138.1, 132.3, 131.1, 131.0, 91.4, 88.5, 72.6, 72.4, 70.0, 69.8, 67.8, 67.7, 61.4, 61.3, 49.6, 49.2, 46.4, 45.7, 45.5, 43.2, 43.0, 42.9, 42.4, 42.3, 30.2, 29.1, 28.4, 20.4-20.6 ($\underline{C}H_3CO$). Anal. Calcd for $C_{22}H_{28}O_{11}$: C, 56.41; H, 6.02. Found: C, 56.67; H, 6.11. FAB-MS. Calcd for $C_{22}H_{28}O_{11}$ $[M+Na]^+$ 491.1529, Found 491.1533.

Methods

*General polymerization procedure with initiator **B** or **C***

A CH_2Cl_2 solution (0.5 mL) containing initiator **B** or **C** (5.35 μmol) was added in one portion to a rapidly stirred CH_2Cl_2 solution (0.5-2.5 mL) containing the prescribed amount of **1** at 25 ºC, and the mixture was stirred for prescribed time. The polymerization was quenched by adding ethyl vinyl ether in excess amount after consumption of the monomers, and the reaction stirred for an additional 1 h for completion (Scheme 2-3). The resultant solution was poured dropwise to a stirred cyclohexane solution (~100 mL), affording pale yellow-grey precipitates. The polymer was collected by filtration, and then dried *in vacuo*. Yield >90 %.



Scheme 2-3. ROMP of monomers **1-2** with initiators $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**) or $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**).

Poly(**1**). ^1H ($CDCl_3$): δ 1.27 (br), 1.59 (br), 1.92, 1.97, 2.30-3.12 (br), 3.76, 3.97, 4.19, 5.02, 5.14, 5.29, 5.57. Resonances at 1.27, 1.59, 2.30-3.12 are due to protons of the five-membered ring (ring-opened norbornene, total 7H), signals at 1.92-1.97 are due to protons for the acetyl groups (12H), signals at 3.76-4.19 are due to protons of the glucose residue (total 3H), signals at 5.14-5.57 are due to protons of the glucose residue and olefinic protons of ring-opened structure (3.79-5.61, total 6H). ^{13}C ($CDCl_3$): δ 172.7, 172.2 (m, C=O), 170.3, 170.1, 169.8, 169.2, 168.9 (CH_3CO), 134.6-135.1, 132.4-132.6, 13.05-130.7, 127.7-128.9, 125.8-125.9 (olefinic), 91.5, 91.3, 72.6, 72.4, 69.8-703, 67.4-67.6, 61.2, (due to the glucose residue), 47.8-48.3, 45.5-46.0, 42.4, 39.0-41.0, 37.3, 35.7, (five-membered ring), 20.3-20.5 (CH_3CO).

Poly(**2**). ^1H ($CDCl_3$): δ 1.29 (br), 1.57 (br), 1.94, 1.96, 1.98, 2.03, 2.05, 2.30-3.12 (br), 3.79, 3.89, 3.96, 4.01, 4.16, 4.37, 4.80, 4.89, 5.26-5.33, 5.61. Resonances at 1.29, 1.57, 2.30-3.12 are due to protons of the five-membered ring (ring-opened norbornene, total 7H), signals at 1.94-2.05 are due to protons for the acetyl groups (21H), signals at 3.79-4.89 are due to protons of the maltose residue (total 7H), signals at 5.26-5.61 are due to protons of the maltose residue and

olefinic protons of ring-opened structure (3.79-5.61, total 9H). ^{13}C ($CDCl_3$): δ 172.1-172.5 (m, C=O), 170.3, 170.1, 170.0, 169.8, 169.7, 169.5, 169.2 (CH_3CO), 134.7, 132.9, 130.8, 129.8, 127.8-128.8, 125.9 (olefininc), 95.5, 91.1, 74.9, 72.7, 72.1-72.4, 71.0, 69.8, 69.3, 68.3, 67.8, 62.2, 61.1 (due to the maltose residue), 47.9, 45.9, 42.4, 39.5-40.8, 37.3, 35.9 (five-membered ring), 20.3-20.7 (CH_3CO).

*Preparation of di-block copolymers with initiator **B***

The basic procedure for the preparation of diblock copolymers was the same as that for preparing the homopolymers except that a CH_2Cl_2 solution (0.5 mL) of monomer **2** (53.5, 80.3, or 107 μmol) was added after consumption of former monomer confirmed by independent homopolymerization runs (by both GPC and ^1H NMR). Yield 92->95 %. The syntheses of multi-block copolymers (runs 17-19) were the same as that for preparing the homopolymers except that a CH_2Cl_2 solution (0.3 mL) of 2nd monomer (53.5 μmol) was added after consumption of the first monomer confirmed by independent polymerization runs (by both GPC and ^1H NMR). The 3rd and 4th monomer (53.5 μmol in CH_2Cl_2 0.3 mL, runs 18-19) were also added to the reaction mixture in the same manner. Yield 92->95 %. Typical ^1H-, ^{13}C-NMR spectra for resultant poly(**1**-*bl*-**2**) are shown in the Supporting Information.

2-3. Results and Discussion

Syntheses of ester-type norbornene derivatives that contain glucose (2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate, **1**) or maltose (2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate, **2**, Scheme 2-2) residues were carried out according to our previous method by esterification of 2,3,4,6-tetra-*O*-acetyl-glucose or 2,3,6-2',3',4',6'-hepta-*O*-acetyl-maltose with norbornene carboxylic acid chloride (*endo*/*exo* = 87/13).[18]

These monomers **1-2** were purified by recrystallization from a mixture of CH_2Cl_2 and hexane chilled at -30 ºC in a drybox, and were obtained as white microcrystals. As pointed out previously, the monomer purity is an especially important requirement for living polymerization using the molybdenum system e.g. $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}^iPr_2C_6H_3)(O^tBu)_2$ (**A**),[14,18] as they are very sensitive to moisture and oxygen. The polymerization of **1-2** using the initiator **A** in toluene proceeded in a living manner and the resultant polymers [poly(**1**), poly(**2**)] possessed M_n values that were very close to those calculated based on monomer/Mo molar ratio with narrow molecular weight distributions (M_w/M_n = <1.2) in all cases.[18]

2-3-1. Living ROMP of norbornenes containing sugars by $Ru(CHPh)(Cl)_2(PCy_3)_2$ (B) initiator

*Preparation of homopolymers with **B***

Polymerizations of **1-2** in CH_2Cl_2 using $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**) initiator were conducted at various monomer/Ru molar ratios under the same conditions (highly purified monomer, anhydrous solvent, under a nitrogen atmosphere in the drybox) for ROMP with molybdenum initiator (**A**). These homopolymers were prepared by adding *n* equivalents of monomer to the initiator, and the polymers were cleaved from the metal with ethyl vinyl ether, a method that is widely employed with initiators of this general type.

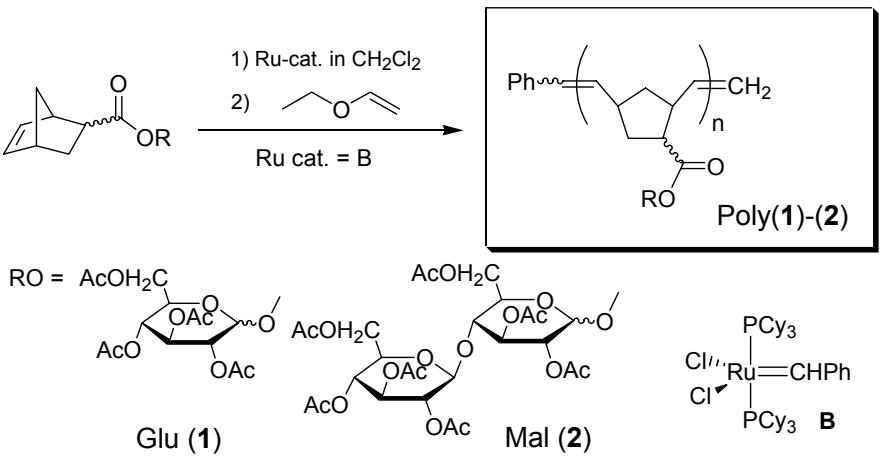
As summarized in Table 2-1, these polymerizations were completion in all cases, with the resultant materials [poly(**1**) and poly(**2**)] possessing narrow molecular weight distributions in all cases (M_w/M_n = 1.04-1.17) confirmed by GPC in THF. It was revealed that the polymerization of **2** with **B** required a longer reaction time (15-25 h was finished for completion), whereas the corresponding polymerization using the molybdenum initiator (**A**) in toluene was finished within 1 h,[18] although *endo* monomers from a mixture of isomers (*endo*/*exo* = 87/13)

often take longer to polymerize than the corresponding *exo* isomers probably due to an unfavorable steric interaction between the monomers and initiating species.[39-41] The M_n values increased at higher monomer/Ru molar ratios as shown in Figure 2-1, and were close to those calculated based on monomer/Ru molar ratios. It seems likely that the polymerization proceeds in a living fashion with high initiation efficiency although the M_n values shown in Table 2-1 are those measured by GPC vs polystyrene standards. This is because the observed M_n values determined by GPC for polymers prepared using the molybdenum initiator (**A**) were in good agreement with those calculated based on monomer/Mo molar ratio which was confirmed by MALDI-TOF mass spectrometry, and this is also because that the M_n value for poly(**1**) based on the integration ratios estimated by ^{1}H NMR spectra (in DMSO-d_6 at 25 ºC, integration of polymer end groups vs internal olefin resonances[10]) was in good agreement with that calculated based on the monomer/Ru molar ratio (run 2), although this method is somewhat difficult to estimate precisely. Based on these results, it is thus suggested that the polymerization of monomer **1** and **2** with **B** took place in a living manner with high initiation efficiency.

Table 2-1. ROMP of monomers **1**-**2** with **B**.[a]

Run No.	Monomer	Equiv.[b]	Time / h	M_n[c] (calcd.) $\times10^{-4}$	M_n[d] (GPC) $\times10^{-4}$	M_w/M_n[d] (GPC)	Yield[e] / %
1	**1**	10	2	0.48	0.77	1.17	>95
2	**1**	20	2	0.95	1.13[f]	1.16	94
3	**1**	25	3	1.18	1.44	1.16	>95
4	**1**	30	3	1.42	1.67	1.15	92
5	**1**	40	4	1.89	2.09	1.15	>95
6	**2**	10	15	0.77	0.92	1.12	94
7	**2**	15	15	1.15	1.27	1.10	>95
8	**2**	20	15	1.53	1.48	1.07	>95
9	**2**	25	25	1.90	1.89	1.05	>95
10	**2**	30	25	2.28	2.24	1.04	92
11	**2**	40	25	3.04	2.75	1.04	>95

[a] Conditions: CH_2Cl_2 1.0 mL, 25 ºC, Ru 5.35 μmol (for **1**, runs 1-5) or 3.30 μmol (for **2**, runs 6-11); [b] Initial monomer/Ru molar ratio; [c] Calculated based on monomer/Ru molar ratio; [d] GPC data in THF vs polystyrene standards; [e] Isolated yield; [f] M_n = 1.24×10^4 (calculated based on ^{1}H NMR spectrum in DMSO-*d*6).



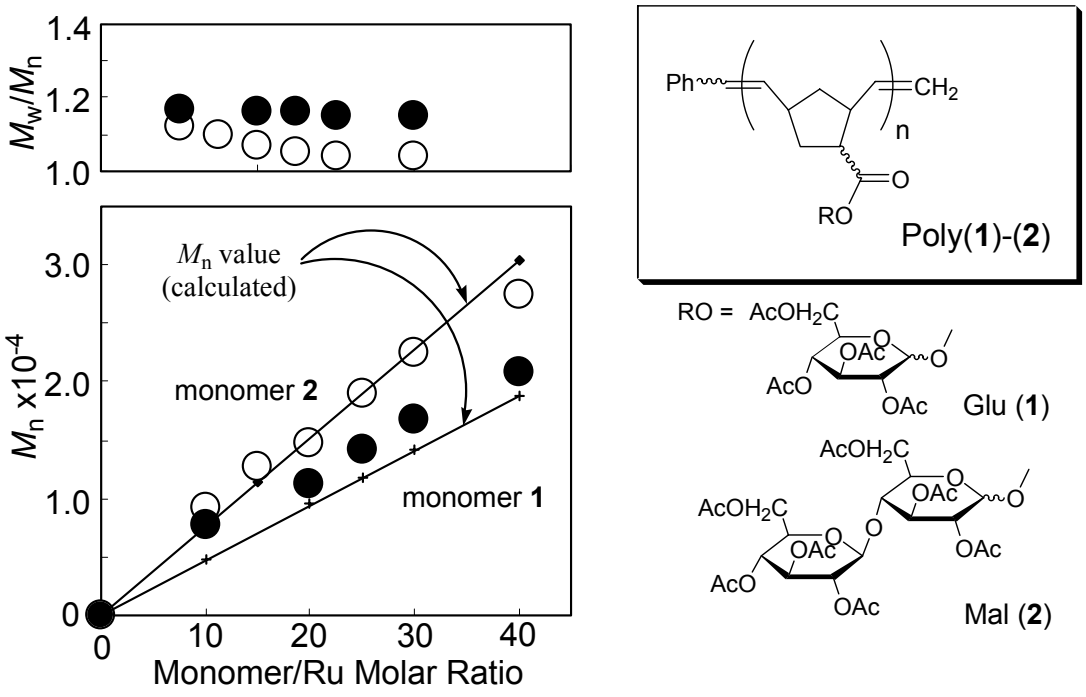


Figure 2-1. Plots of M_n, M_w/M_n vs monomer/Ru molar ratios (based on results in Table 2-1) for the ROMP of **1** (●) or **2** (○) with **B** in CH_2Cl_2 at 25 ºC.

*Post-polymerization of norbornenes containing glucose **1** with **B***

In order to confirm that the polymerizations initiated with **B** were living, in particular to confirm that the polymer-chain end was still living after consumption of the monomer, a post polymerization was conducted after the consumption of the initial monomer. Monomer **1** (20 equiv.) was added to the reaction mixture after consumption of 20 equiv. of **1**, and the M_n value (Table 2-2, run 12) for resultant poly(**1**) was the same as that calculated from the monomer/Ru molar ratio and to that obtained by the polymerization of 40 equiv. of **1** (run 5). As shown in Figure 2-2, the elution peak in the GPC trace (run 2, $M_n = 1.13\times10^4$, $M_w/M_n = 1.16$) shifted towards the higher molecular weight region maintaining a narrow peak width (run 12, $M_n = 2.10\times10^4$, $M_w/M_n = 1.15$) after the consumption of the 2nd monomer, and the GPC trace for poly(**1**) after the post polymerization was the same as the corresponding homopolymer obtained from 40 equivalents of **1** (run 5, $M_n = 2.09\times10^4$, $M_w/M_n = 1.15$). Based on these results, it is clear that the present

polymerization takes place in a living fashion.

Table 2-2. Post-polymerization of monomer **1** with **B**.[a]

Run No.	Equiv.[b]	Time / h	M_n[c] (calcd.) $\times 10^{-4}$	M_n[d] (GPC) $\times 10^{-4}$	M_w/M_n[d] (GPC)	Yield[e] / %
2	20	2	0.95	1.13	1.16	94
5	40	4	1.89	2.09	1.15	>95
12[f]	20+20	2+4	1.89	2.10	1.15	>98

[a] Conditions: CH_2Cl_2 1.0 mL, 25 ºC, Ru 5.35 μmol; [b] Molar ratio based on monomer/Ru; [c] Calculated value based on monomer/Ru molar ratio; [d] GPC data in THF vs polystyrene standards; [e] Isolated yield; [f] 2nd monomer (107 μmol in CH_2Cl_2 0.5 mL) was added after consumption of the 1st monomer (run 12).

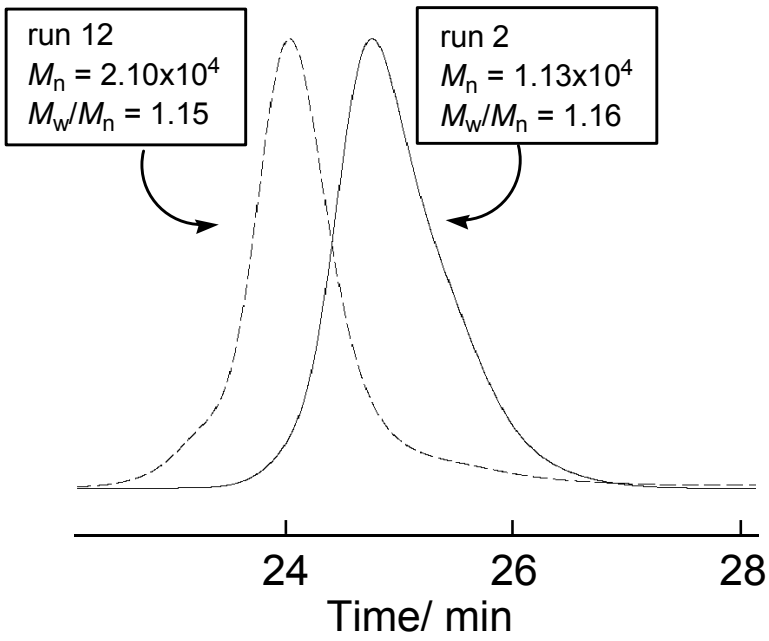


Figure 2-2. GPC traces for post-polymerization of **1** with **B** in CH_2Cl_2 at 25 ºC (runs 2 and 12, Table 2-2).

*Preparation of multiblock copolymers with **B***

Since the present polymerization promoted by **B** proceeds in a living manner, syntheses of various block copolymers were investigated by adding monomers sequentially after consumption of the previous monomer. As shown in Table 2-3, various di-, tri- and tetra-block copolymers consisting of **1** and **2** could be prepared under these polymerization conditions. The molecular weight distributions for resultant copolymers were narrow in all cases (M_w/M_n = 1.05-1.19), and the M_n values were close to those calculated based on monomer/Ru molar ratios. As exemplified in Figure 2-3, the elution peaks in the GPC traces shifted toward higher molecular weight values upon the addition of monomers maintaining narrow peak widths (from the homopolymer to the tetra-block copolymer). This result clearly indicates that catalyst deactivation was not observed during the polymerization under these well controlled (*perfectly* anhydrous, under inert atmosphere) conditions. Although preparation of multi-block ROMP copolymers containing sugars by the molybdenum initiators were known by us,[14,18] this is still a rare example of preparing block copolymers containing carbohydrates especially using the ruthenium initiator (**B**) which is rather more easy to handle in comparison with the molybdenum allkylidene initiator (**A**) .

Table 2-3. Preparation of multi-block copolymers.[a]

Run No.	Monomer 1st/2nd/3rd/4th	Equiv.[b] 1st/2nd/3rd/4th	Time / h	M_n[c] (calcd.) $\times10^{-4}$	M_n[d] (GPC) $\times10^{-4}$	M_w/M_n[d] (GPC)	Yield[e] / %
13[f]	**1/2**	20/10	2/17	1.71	2.07	1.08	92
14[f]	**1/2**	20/15	2/17	2.08	2.36	1.05	>95
15[f]	**1/2**	20/20	2/17	2.46	2.75	1.04	>95
16	**1**	15	2	0.71	1.02	1.16	92
17[g]	**1/2**	15/10	2/19	1.47	1.81	1.13	>95
18[g]	**1/2/1**	15/10/10	2/19/4	1.94	2.29	1.19	>95
19[g]	**1/2/1/2**	15/10/10/10	2/19/4/24	2.70	2.72	1.13	>95

[a] Conditions: CH_2Cl_2 1.0 (runs 13-15) or 0.6 (runs 16-19) mL, 25 ºC, Ru 5.35 μmol (for **1**); [b] Molar ratio based on monomer/Ru; [c] Calculated value based on monomer/Ru molar ratio; [d] GPC data in THF vs polystyrene standards; [e] Isolated yield; [f] 2nd monomer (53.5, 80.3, and 107 μmol in CH_2Cl_2 0.5 mL) was added after the consumption of the 1st monomer (runs13-15); [g] 2nd monomer (53.5 μmol in CH_2Cl_2 0.3 mL), 3rd monomer (53.5 μmol in CH_2Cl_2 0.3 mL, runs 18-19), and 4th monomer (53.5 μmol in CH_2Cl_2 0.3 mL, run 19) were added after the consumption of the previous monomer.

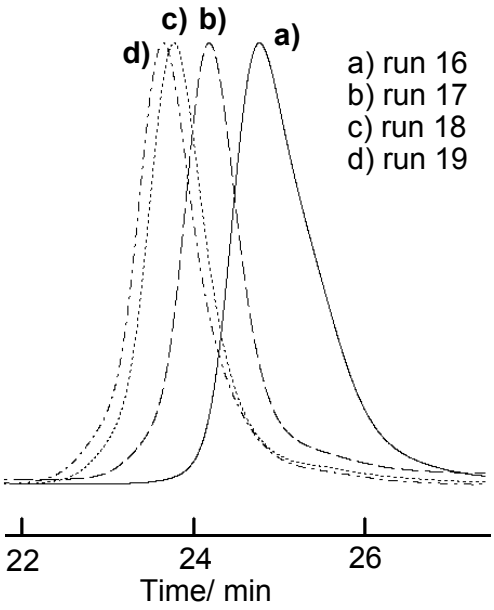


Figure 2-3. GPC traces for synthesis of multi-block copolymers containing **1-2** with **B** in CH_2Cl_2 at 25 ºC (runs 16-19, Table 2-3).

2-3-2. ROMP of Norbornenes Containing Sugars by $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (C) Initiator.

Polymerizations of **1**-**2** in CH_2Cl_2 using $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**) initiator were preformed at various monomer/Ru molar ratios, and ethyl vinyl ether was used to terminate the polymerization. These polymerizations were completed within 1 h in all cases (Table 2-4), whereas the polymerization of **2** with **B** required 15 h for complete monomer consumption under the same conditions (run 8 vs runs 24-25). Resultant polymers possessed higher M_n values than those calculated based on monomer/Ru molar ratios in all cases and the molecular weight distributions were somewhat broad (M_w/M_n = 1.65-1.98), whereas the M_n values obtained by **B** were almost identical to those calculated from the monomer/Ru molar ratio with narrow distributions. In addition, these values (M_n, M_w/M_n) were not affected by the initial monomer concentration, or the time course. The probable reason for the higher M_n values coupled with the broad distributions is the rapid propagation with the imperfect initiation efficiency under these polymerization conditions.[26]

The polymerizations of **1** by **C** were performed at varying monomer/Ru molar ratios (Table 2-5). The M_n value for poly(**1**) increased upon increasing the monomer/Ru molar ratios although the molecular weight distributions were somewhat broad in all cases (M_w/M_n = 1.49-1.94). It should be noted that the polymerization with 1000 equivalent of **1** completed after 1 h (run 32), and the polymerization completed after 2 h even at lower monomer concentration conditions (run 38). These results clearly show that high molecular weight ROMP polymers containing carbohydrate residue can be prepared by using this technique,[31] since the ruthenium initiator (**C**) exhibits better reactivity toward cyclic olefins in addition to its tolerance of impurities (moisture and oxygen) compared to the molybdenum initiator (**A**). Reasons why the M_n values vs polystyrene standards for resultant poly(**1**) were similar to the calculated values in

the polymerizations with 1000 equivalents of **1** are not clear at this moment.[42]

Table 2-4. ROMP of monomer **1**-**2** with **C**.[a]

Run No.	Monomer	$[M]_0$[b] mmol/mL $\times10^{-2}$	Time / h	M_n[c] (GPC) $\times10^{-4}$	M_w/M_n[c] (GPC)	Yield[d] / %
20	**1**	10.7	1	4.36	1.94	92
21	**1**	10.7	3	4.36	1.95	93
22	**1**	3.57	1	4.29	1.88	>95
23	**1**	3.57	3	4.48	1.98	>95
24	**2**	6.60	1	4.18	1.95	>95
25	**2**	6.60	3	4.13	1.82	>95
26	**2**	2.20	1	3.98	1.65	94
27	**2**	2.20	3	4.15	1.82	94

[a] Conditions: CH_2Cl_2 1.0 (runs 20-21, 24-25) or 3.0 (runs 22-23, 26-27) mL, 25 ºC, Ru 5.35 μmol (for **1**, runs 20-23) or 3.30 μmol (for **2**, runs 24-27), monomer (**1** or **2**)/Ru = 20 (molar ratio), calculated M_n (based on molar ratio) = 9500 (for **1**), 1.53×10^4 (for **2**), respectively; [b] Initial monomer concentration mmol/mL; [c] GPC data in THF vs polystyrene standards; [d] Isolated yield.

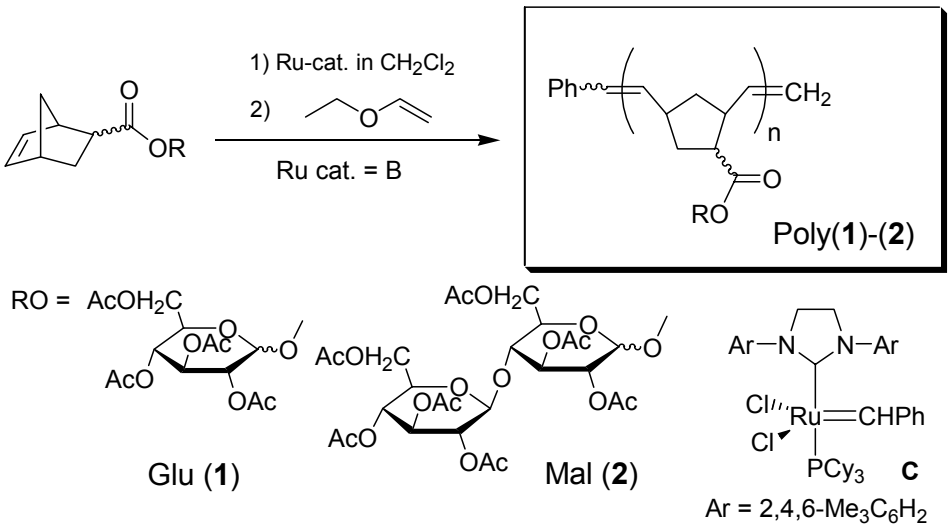


Table 2-5. ROMP of monomer **1** with **C**.[a]

Run No.	Equiv.[b]	$[M]_0$[c] mmol/mL $\times10^{-2}$	Time / h	M_n[d] (calcd.) $\times10^{-4}$	M_n[e] (GPC) $\times10^{-4}$	M_w/M_n[e] (GPC)	Yield[f] / %
28	10	10.7	1	0.48	2.67	1.84	92
20	20	10.7	1	0.95	4.36	1.94	92
29	30	10.7	1	1.42	4.78	1.81	>95
30	40	10.7	1	1.89	5.21	1.81	>95
31	100	10.7	1	4.70	15.1	1.82	>95
32	1000	10.7	1	46.9	45.2	1.49	>95
33	10	3.57	1	0.48	2.48	1.77	92
22	20	3.57	1	0.95	4.29	1.88	>95
34	30	3.57	1	1.42	4.82	1.71	>95
35	40	3.57	1	1.89	5.23	1.84	>95
36	100	3.57	1	4.70	15.1	1.66	>95
37	1000	3.57	1	46.9	29.7	1.48	---[g]
38	1000	3.57	2	46.9	50.9	1.49	>95

[a] Conditions: CH_2Cl_2 1.0 (runs 20, 28-32) or 3.0 (runs 22, 33-38) mL, 25 ºC, Ru 0.107-10.7 μmol, **1** 107 μmol ; [b] Initial monomer/Ru molar ratio; [c] Initial monomer concentration mmol/mL; [d] Calculated by monomer/Ru molar ratio; [e] GPC data in THF vs polystyrene standards; [f] Isolated yield; [g] Polymerization did not complete.

2-4. References and Notes

1. Mann, D. A.; Kiessling L. L. In *Glycochemistry*; Wang, P. G.; Bertozzi, C. R., Eds.; Marcel Dekker: NewYork, 2001; pp 221-275.
2. Lee, Y.; Lee, R. *Acc. Chem. Res.* **1995**, *28*, 321-327.
3. Drickamer, K.; Taylor, M. E. *Ann. Rev. Cell Biol.* **1993**, *9*, 237-264.
4. Varki, A. *Glycobiology* **1993**, *3*, 97-130.
5. Kiessling, L. L.; Strong, L. E. In *Alkene Metathesis in Organic Synthesis*; Fürstner, A. Ed.; Springer-Verlag: Berlin, 1998; pp199-231. Typical reports for synthesis of carbohydrate-based (neobio) polymers are cited therein.
6. Kiessling, L. L.; Owen, R. M. In *Handbook of Metathesis*: Grubbs R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol. 3, pp180-225.
7. Mortell, K. H.; Gingas, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **1994**, *116*, 12053-12054.
8. Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297-2298.
9. Manning, D. D.; Strong, L. E.; Hu, X.; Beck, P. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 3161-3162.
10. Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931-9932.
11. Gordon, E. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30-31.
12. Cairo, C. W.; Gestwicki, J. E.; Kanai, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 1615-1619.
13. Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922-14933.
14. Nomura, K.; Schrock, R. R. *Macromolecules* **1996**, *29*, 540-545.
15. Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248-7255.
16. Meier, S.; Reisinger, H.; Haag, R.; Mecking, S.; Müllhaupt, R.; Stelzer, F. *Chem. Commun.* **2001**, 855-856.

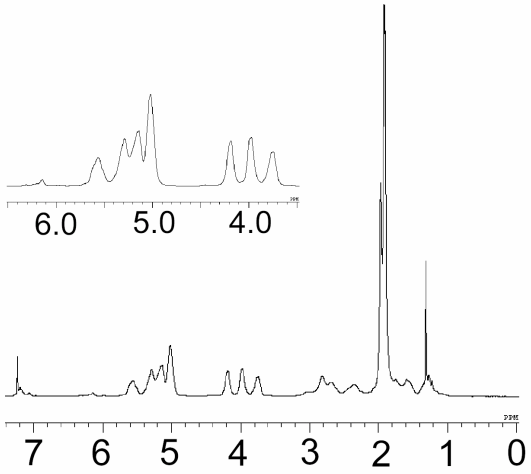
17. Iyer, S.; Rele, S.; Grasa, G.; Nolan, S.; Chaikof, E. L. *Chem. Commun.* **2003**, 1518-1519. In this paper, the molecular weight distribution (M_w/M_n) of a hyaluronan neoglycopolymer prepared with $(IMesH_2)(Cy_3P)RuCl_2(CHPh)$ (**C**) was 1.17 and the average degree of the monomer repeating unit estimated by ^1H NMR was 15.5 (the initial molar ratio of the monomer/Ru was 20).
18. Nomura, K.; Sakai, I.; Imanishi, Y.; Fujiki, M.; Miyamoto, Y. *Macromol. Rapid Commun.* **2004**, *25*, 571-576.
19. In most cases, the degree of polymerization (the molecular weight of the resultant polymers) was only determined by the NMR integration ratio of the polymer end group versus internal olefin resonances, and the molecular weight distributions were not described.
20. Some of these results were presented at the *15th International Symposium on Olefin Metathesis and Related Chemistry* (Kyoto, Japan, Aug, 2003; paper 06).
21. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18-29.
22. Nguyen, S.T.; Trnka, T. M. In *Handbook of Metathesis*; Grubbs, R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol. 3, pp 61-85.
23. Sanfold, M. S.; Love, J. A. In *Handbook of Metathesis*; Grubbs, R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol. 3, pp 112-131.
24. Frenzel, U.; Nuyken, O. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2895–2916.
25. Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903–2906.
26. Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.
27. Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103-10109.
28. Holland, M. G.; Griffith, V. E.; France, M. B.; Desjardins, S. G. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 2125–2131.

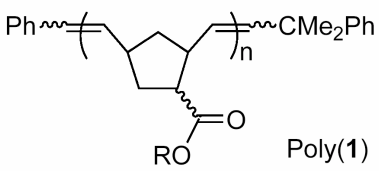
29. Gibson, V. C.; Marshall, E. L.; North, M.; Robson, D. A.; Williams, P. J. *Chem. Commun.* **1997**, 1095-1096.
30. North, M. In *Ring-Opening Metathesis Polymerisation and Related Chemistry*; Khosravi, E.; Szymanska-Buzar, T., Eds.; Kluwer: Dordrecht, 2002; pp 157-166 and pp 167-176.
31. As described by Kiessling in ref. 6 (as unpublished results), the molecular weight distributions for an acetylated polymer[10] with a degree of polymerization 10 were less than or equal to 1.2, and the polymers with a degree of polymerization greater than 50 could not be generated under these conditions.
32. Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378-8387.
33. Bazan, G. C.; Oskam, J. H.; Cho, H.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899-6907.
34. Komiya, Z.; Pugh, C.; Schrock, R.R. *Macromolecules* **1992**, *25*, 6586-6592.
35. Sinner, F.; Buchmeiser, M. R.; Tessadri, R.; Mupa, M.; Wurst K.; Bonn, K. *J. Am. Chem. Soc.* **1998**, *120*, 2790-2797.
36. Rowell, R.M.; Feather, M.S. *Carbohyd. Res.* **1967**, *4*, 486-491.
37. Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohyd. Res.* **1977**, *39*, 368-373.
38. Khan, R.; Konowicz, P.A.; Gardrossi, L.; Matulova, M.; de Gennaro, S. *Aust. J. Chem.* **1996**, *49*, 293-298.
39. Biagini, S. C. G..; Coles, M. P.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; North, M. *Polymer*, **1998**, *39*, 1007-1014.
40. Maynard, H. D.; Okada, S. Y.; Grubbs, R. H. *Macromolecules*, **2000**, *33*, 6239-6248.
41. Pollino, J. M.; Stubbs, L. P.; Weck, M. *Macromolecules*, **2003**, *36*, 2230-2234.
42. As described in ref 26, the initiation rate with **C** (at 35 ºC) was about 300

times slower than that with **B** (at 25 ºC) in CH_2Cl_2. Because the initiation rate was also dependent on the initial monomer concentration, it seems likely that this would be the reason for the observation in this article.

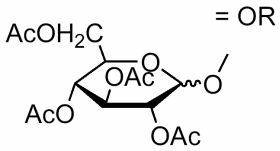
2-5. Supporting Information

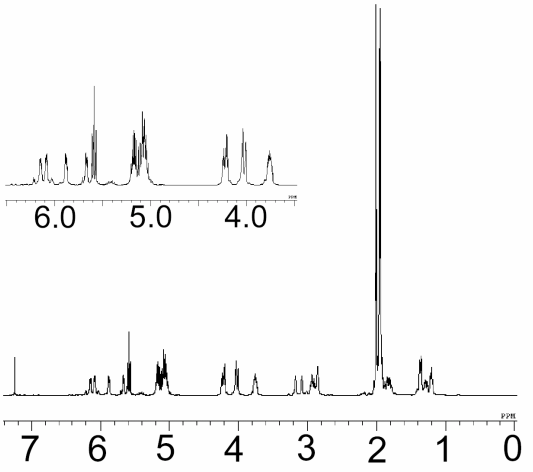
^{1}H NMR Spectra (in $CDCl_3$ at 25 ^oC) for monomer **1**, and poly(**1**)

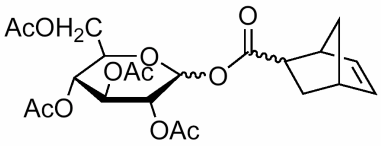




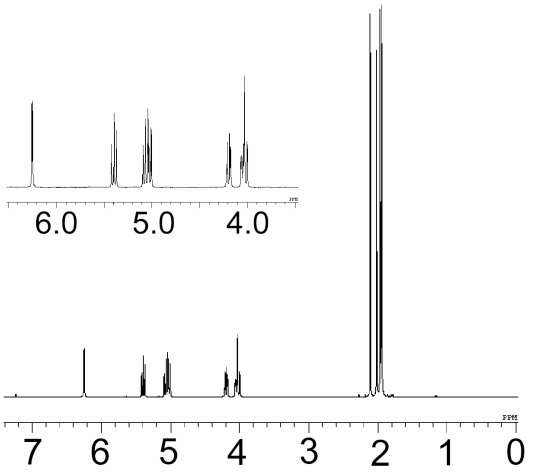
Poly(**1**)

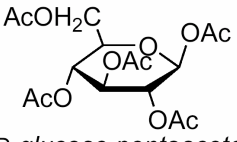






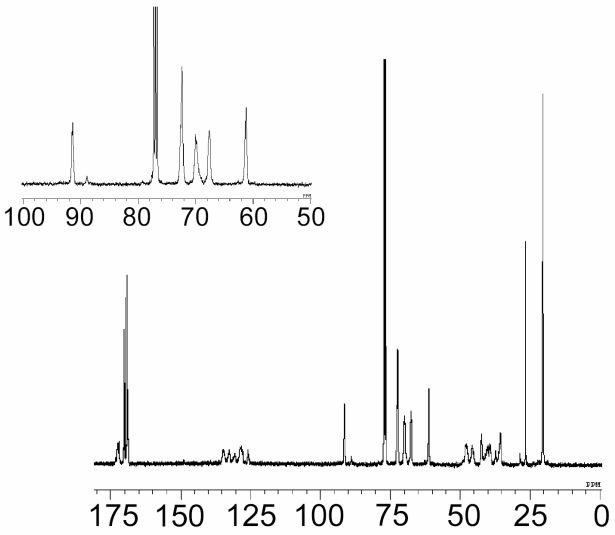
2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylayte (**1**)

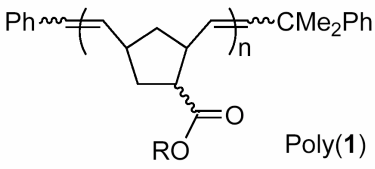


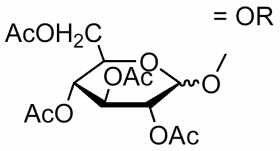


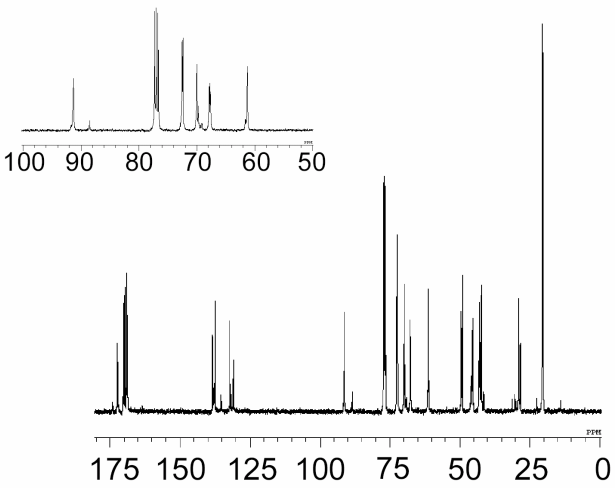
β-D-glucose pentaacetate

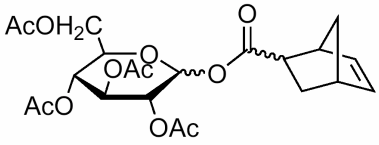
^{13}C NMR Spectra (in $CDCl_3$ at 25 ^{o}C) for monomer **1**, and poly(**1**)



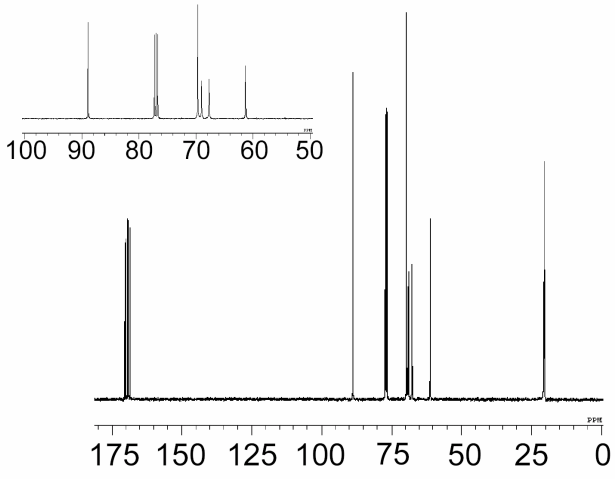


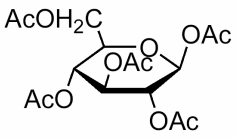






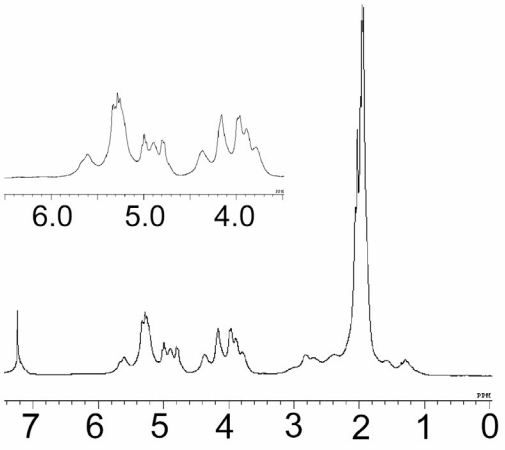
2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate (**1**)

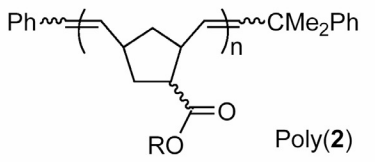




β-D-glucose pentaacetate

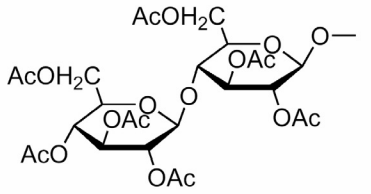
^{1}H NMR Spectra (in $CDCl_3$ at 25 ^oC) for monomer **2**, and poly(**2**)

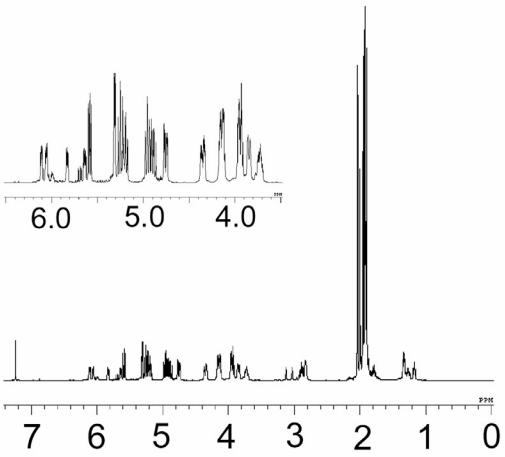


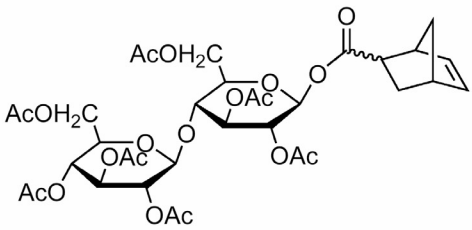


Poly(**2**)

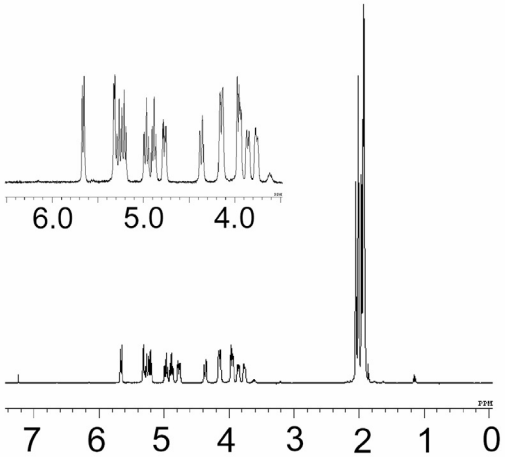
= OR

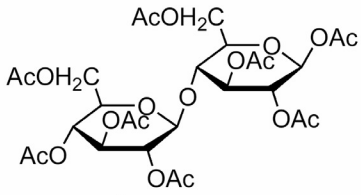






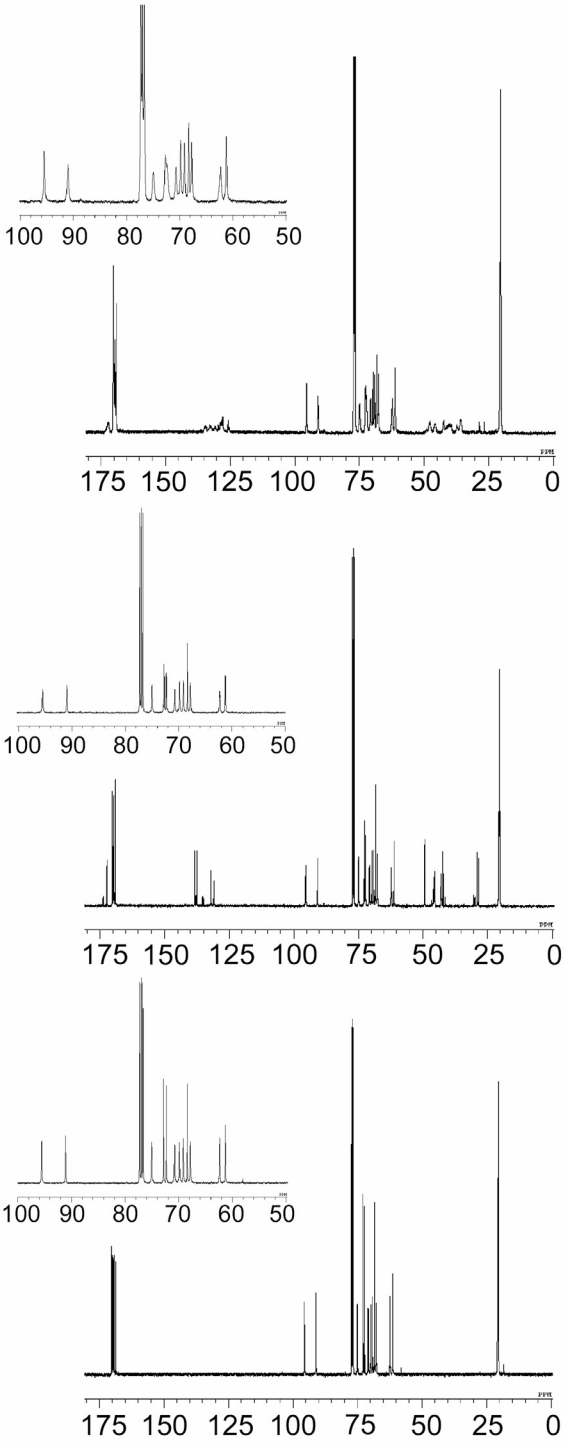
2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2- carboxylate (**2**)

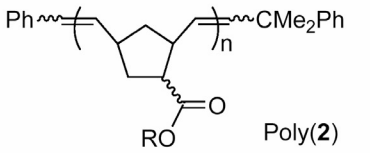




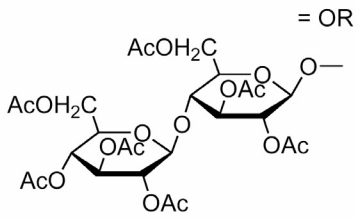
D-maltose octaacetate

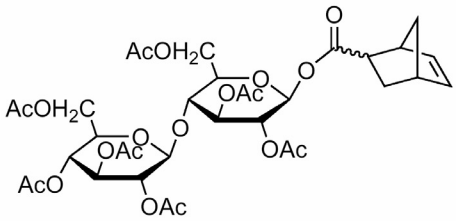
^{13}C NMR Spectra (in $CDCl_3$ at 25 ^{o}C) for monomer **2**, and poly(**2**)



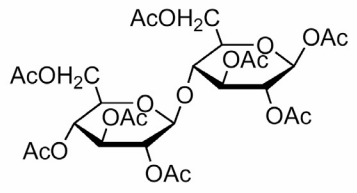


Poly(**2**)



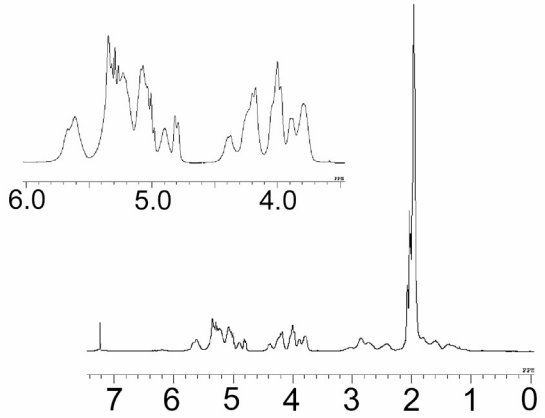


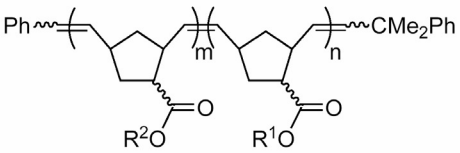
2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2- carboxylate (**2**)



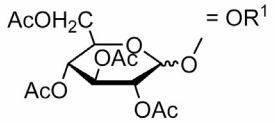
D-maltose octaacetate

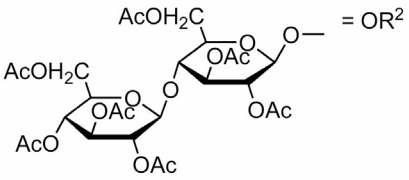
^{1}H and ^{13}C NMR Spectra (in $CDCl_3$ at 25 ^oC) for poly(**1**-*bl*-**2**)

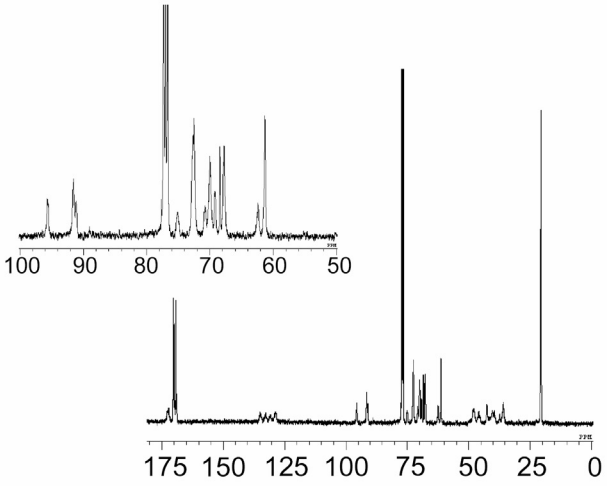


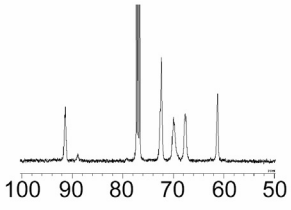


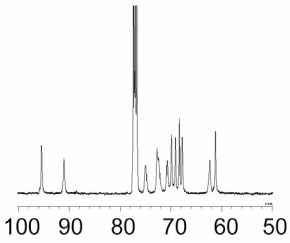
Poly(**1**-*bl*-**2**)

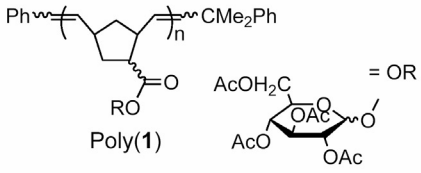




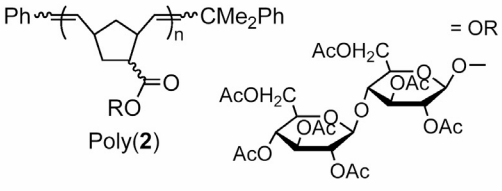








Poly(**1**)



Poly(**2**)

Chapter 3

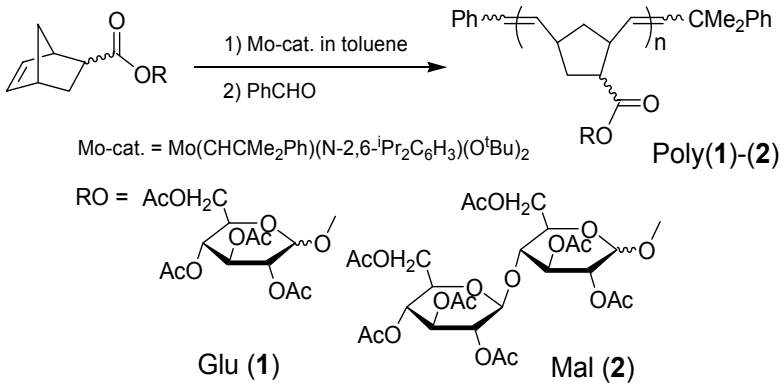
Evaluation of the Rate Constants for the ROMP of Norbornenes Containing Sugars Promoted by Well-Defined Molybdenum and Ruthenium Complexes

Contents

3-1. Introduction

In the previous chapter, the ROMP technique using ruthenium $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**) and $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**) initiators was shown to be an effective method of preparing homopolymers and multi-block copolymers that contain acetyl-protected maltose (disaccharide) or glucose (monosaccharide) residues. Resultant polymers containing carbohydrate were the precise control and very high of molecular weight. The ROMP with **B** took place not only in a living fashion (M_w/M_n = <1.17) but also with almost quantitative initiation.

The living ROMP technique with a Schrock-type molybdenum-alkylidene initiator, $Mo(N\text{-}2,6\text{-}^iPr_2C_6H_3)(CHCMe_2Ph)(O^tBu)_2$ (**A**), has been reported to be an effective method for preparing homopolymers and multiblock copolymers containing acetal-protected monosaccharide residues such as galactose, ribose, and mannose.[1] More recently, we reported that this technique is also effective for the preparation of homopolymers and diblock copolymers that contain acetyl-protected glucose [monosaccharide; i.e., 2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate (**1**)] or maltose [disaccharide; i.e., 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate (**2**)] residues (Scheme 3-1) and that these polymerizations take place not only in a living fashion [weight-average molecular weight/number-average molecular weight (M_w/M_n) < 1.2] but also with almost quantitative initiation.[2,3] Although examples of the synthesis of bioactive polymers by ROMP with ruthenium initiators are widely known,[4–17] as far as we know, examples comparing the initiator performances under the same conditions (especially for ROMP) are limited.[18–20]



Scheme 3-1

A comparison of these initiators under the same conditions is important for designing better initiators and for preparing desired polymers in a controlled fashion. Therefore, in this chapter, we present our results comparing the performances for ROMP initiated with welldefined molybdenum (**A**) and ruthenium (**B** and **C**) initiators under the same conditions (Chart 3-1).

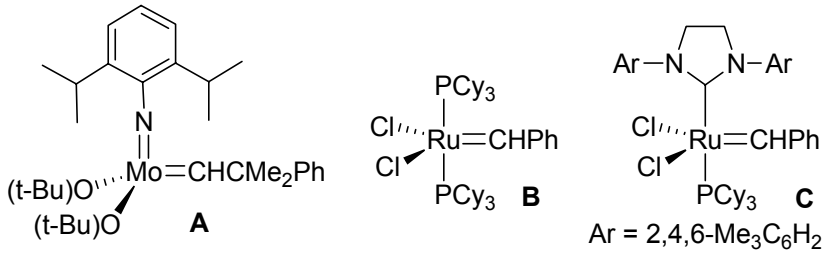
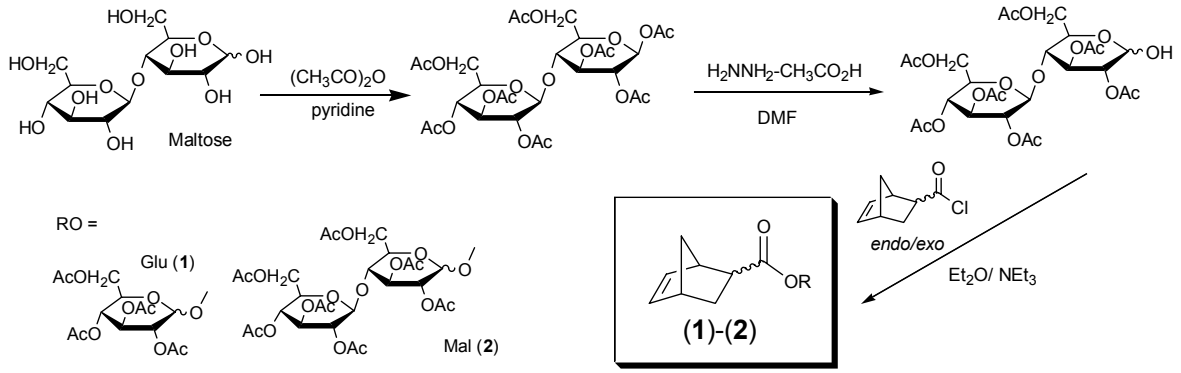


Chart 3-1. Molybdenum (**A**) and ruthenium (**B** and **C**) initiators.

3-2. Experimental

Materials

The molecular structures of ester-type norbornene derivatives containing carbohydrates are shown in Scheme 3-2. Synthesis procedures for monomers **1**-**2** were described in chapter 2.



Scheme 3-2. Synthesis of ester-type norbornene derivatives containing glucose (**1**), and maltose (**2**).

Methods

General procedures with initiators **B** or **C** are described in chapter 2.

*General polymerization procedure with initiator **A** (Scheme 3-1)*

A toluene solution (0.5 mL) containing initiator **A** (5.35 μmol) was added in one portion to a rapidly stirred toluene solution (2.5-11.5 mL) containing the prescribed amount of **1** at 25 ºC, and the mixture was stirred for reported time. The polymerization was quenched by adding excess PhCHO after consumption of the monomers, and was stirred for an additional 1 h for completion, although termination usually takes place rapidly. The resultant solution was poured dropwise to a stirred cyclohexane solution (~100 mL), affording white - pale yellow precipitates. The polymer was collected by filtration, and was then dried *in vacuo*. Yield >90 %.

*General procedure for NMR scale polymerization of **1-2** with **B** or **C***

Typical experimental procedures are as follows. Monomer **1** (107 μmol in $CDCl_3$ or toluene-d_8 0.8 mL) in a NMR tube was capped with a rubber septum in the drybox, and was then placed in a liquid nitrogen dewar bath. Initiator **B** or **C** (5.35-1.78 μmol) dissolved in $CDCl_3$ or toluene-d_8 (0.2 mL) was then added slowly to the above NMR tube via a syringe. The sample was then placed directly into the NMR instrument kept at 25 ºC. The polymerization was monitored by ^{1}H NMR spectroscopy, and the monomer conversion during the prescribed time was estimated based on the integration ratio of the (cyclic) olefinic proton resonances (at 6.14-5.64 ppm) and the resonances in the acetyl group (at 2.05-1.92 ppm). The reaction time used for the calculation was that at the middle of accumulation.

3-3. Results and Discussion

3-3-1. Time Course and Monomer Concentration Dependences for the ROMP with Mo(N-2,6-$^{i}Pr_2C_6H_3$)(CHCMe$_2$Ph)(O^{t}Bu)$_2$ (A), Ru(CHPh)(Cl)$_2$(PCy$_3$)$_2$ (B), and Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$) (C) Initiators using GPC Analysis

*ROMP of **1-2** with **B** and **C** in CH_2Cl_2*

The dependences of the time course for the polymerizations of **1**-**2** with **B** under two initial monomer concentration conditions (monomer/Ru molar ratio = 20, in CH_2Cl_2 at 25 ºC) is summarized in Table 3-1 and Figure 3-1. As described below, the polymerizations of **1** took place rather more efficiently than those of **2**, with narrow molecular weight distributions in all cases (M_w/M_n = 1.07-1.16). The degree of polymerization at a certain time was strongly affected by the initial monomer concentration, and the polymerization of **2** was not completed even after 6 h (run 62). Since we reported that these polymerizations with the molybdenum initiator (**A**) in toluene were completed within 30 min even at low monomer concentration conditions, as described below,[2] the optimization of the monomer concentration is thus key to the completion of the polymerization especially when using the ruthenium initiator **B**.

Based on the results shown below (Table 3-1 and Figure 3-1), time-course plots vs calculated $\ln[M]/[M]_0$ values[21] in particular at relatively low monomer conversion conditions (in polymerization runs started at low initial monomer concentrations) were investigated in order to estimate the propagation rate as well as the order of monomer concentration toward the propagation rate (Figure 3-2).[22] Linear first order dependencies were observed in both cases (marked with ■ for **1**, and ◆ for **2**, respectively), clearly indicating that first order dependencies between the propagation rates and the monomer concentrations are present. Rate constants, k values (by **B** in CH_2Cl_2 for **1**-**2** at 25 ºC), were estimated [$k_{\mathbf{1}(\mathbf{B},CH2Cl2)} = 8.6\times10^{-3}$ min^{-1}, $k_{\mathbf{2}(\mathbf{B},CH2Cl2)} = 2.5\times10^{-3}$ min^{-1} for the ROMP of **1**-**2**, respectively] based on these results, as a first order monomer concentration dependence toward the propagation rates were observed.[23] Attempts to estimate the monomer concentration dependence as well as k values for polymerization of **1** with **C** was unsuccessful, as the polymerization was almost complete within 15 min (runs 50-52, under the same conditions as in runs 45-49, Table 3-1).

Table 3-1. Time course for ROMP of monomer **1-2** initiated with **B** or **C**. [a]

Run No.	Monomer	Ru	$[M]_0$[b] mmol/mL $\times 10^{-2}$	Time / min	M_n[c] (GPC) $\times 10^{-4}$	M_w/M_n[c] (GPC)	Conv.[d] (^{1}HNMR) / %	Yield[e] / %
39	**1**	**B**	10.7	5	0.40	1.14		---[f]
40	**1**	**B**	10.7	10	0.48	1.15		---[f]
41	**1**	**B**	10.7	20	0.63	1.12	60	---[f]
42	**1**	**B**	10.7	40	0.77	1.12	68	---[f]
43	**1**	**B**	10.7	60	0.94	1.11	80	(94)[f]
2	**1**	**B**	10.7	120	1.13	1.16	>97	94
44	**1**	**B**	10.7	180	1.13	1.16	>97	>95
45	**1**	**B**	3.57	30	0.48	1.14	40	---[f]
46	**1**	**B**	3.57	60	0.65	1.16	50	---[f]
47	**1**	**B**	3.57	120	0.76	1.12		---[f]
48	**1**	**B**	3.57	180	0.92	1.14	81	---[f]
49	**1**	**B**	3.57	360	1.07	1.15	>97	>95
50	**1**	**C**	3.57	5	3.20	1.63	87	---[f]
51	**1**	**C**	3.57	15	3.90	1.66	93	---[f]
52	**1**	**C**	3.57	30	4.35	1.86	>97	>95
22	**1**	**C**	3.57	60	4.29	1.88	>97	>95
53	**2**	**B**	6.60	30	0.71	1.13	48	---[f]
54	**2**	**B**	6.60	60	0.84	1.12	58	---[f]
55	**2**	**B**	6.60	120	1.00	1.12	66	---[f]
56	**2**	**B**	6.60	180	1.25	1.09	85	---[f]
57	**2**	**B**	6.60	360	1.40	1.11	95	>95
58	**2**	**B**	6.60	720	1.42	1.10	>97	>95
8	**2**	**B**	6.60	900	1.48	1.07	>97	>95
59	**2**	**B**	2.20	30	0.51	1.11	34	---[f]
60	**2**	**B**	2.20	60	0.61	1.11	40	---[f]
61	**2**	**B**	2.20	180	0.89	1.13	57	---[f]
62	**2**	**B**	2.20	360	1.08	1.12	72	---[f]

[a] Conditions: CH_2Cl_2 1.0 (runs 2, 8, 39-44, 53-58) or 3.0 (runs 22, 45-52, 59-62) mL, 25 ºC, Ru 5.35 μmol (for **1**) or 3.30 μmol (for **2**), monomer/Ru = 20 (molar ratio), calculated M_n (based on molar ratio) = 9500 (for **1**) or 1.53×10^4 (for **2**), respectively; [b] Initial monomer concentration mmol/mL; [c] GPC data in THF vs polystyrene standards; [d] Conversion estimated by ^{1}H NMR; [e] Isolated yield; [f] The polymerization did not complete, and the yields were based on a mixture of the monomer and polymer.

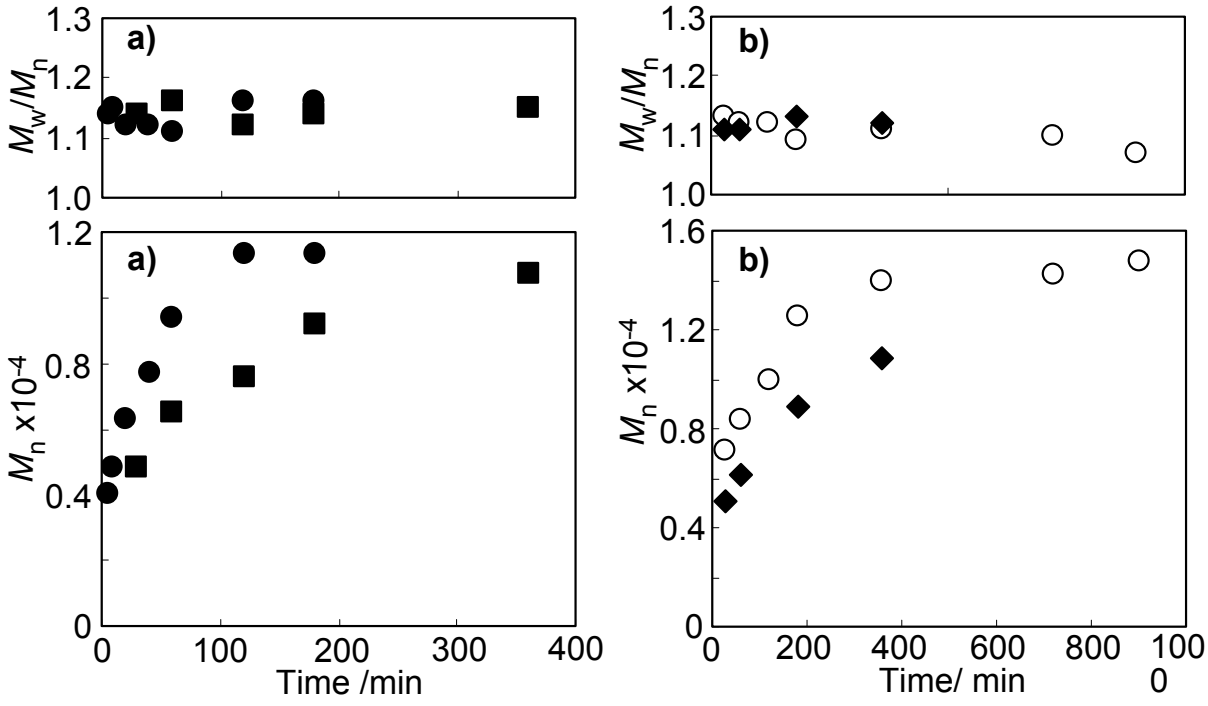
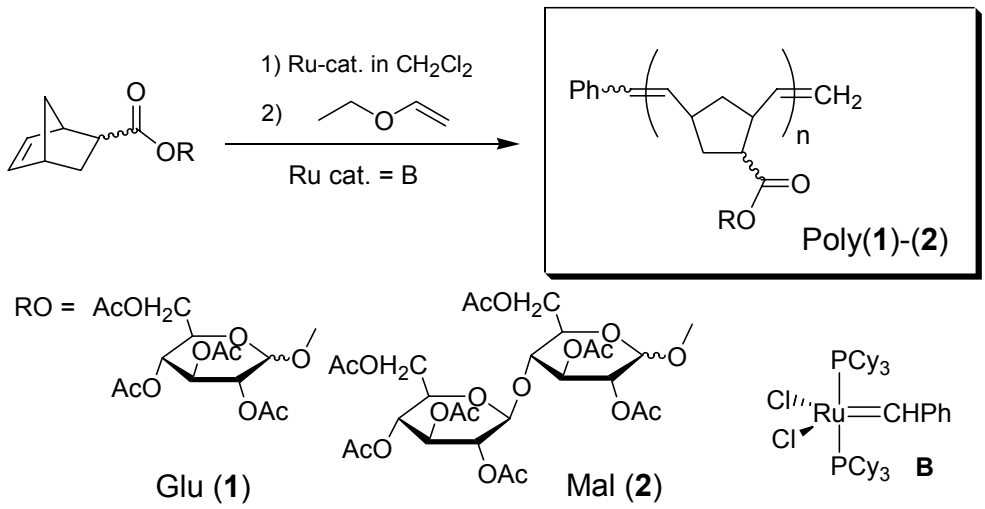


Figure 3-1. Time-course plots vs M_n values for the polymerization of (a) **1**, (b) **2** with **B** in CH_2Cl_2 at 25 ºC (molar ratio of monomer/Ru = 20). The initial monomer concentration: 1.07×10^{-1} (●, monomer **1**), 3.57×10^{-2} (■, monomer **1**), 6.60×10^{-2} (○, monomer **2**), and 2.20×10^{-2} (◆, monomer **2**) mmol/mL, respectively.



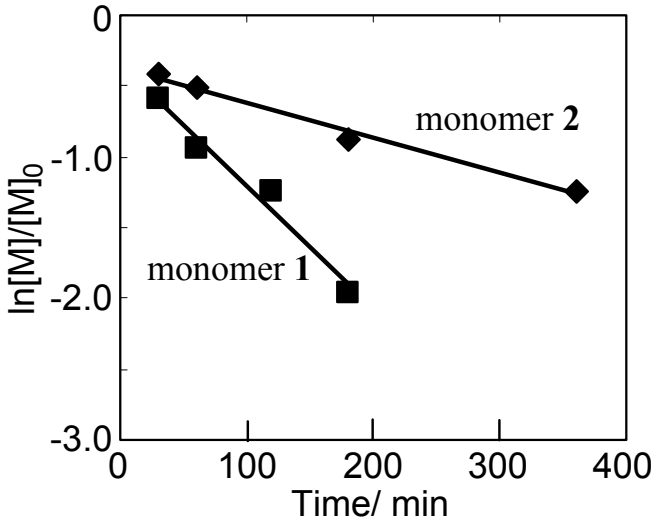


Figure 3-2. Time-course plots vs ln[M]/[M]$_0$ for the polymerization of **1**-**2** with **B** in CH_2Cl_2 at 25 ºC (molar ratio of monomer/Ru = 20) based on results shown in Figure 3-1 and Table 3-1. The initial monomer concentration, [M]$_0$: 3.57×10^{-2} (■, monomer **1**), 2.20×10^{-2} (◆, monomer **2**) mmol/mL, respectively.

*ROMP of **1**-**2** with **A**, **B**, and **C** in toluene*

In order to compare the initiator performances, the polymerizations of **1**-**2** using the molybdenum (**A**) and ruthenium (**B**, **C**) initiators were conducted in toluene (Table 3-2).[24] The polymerization with **A** using 20 equivalents of **1** was complete within 15 min under the same initial monomer concentration conditions (runs 63-64) that were performed with **B** and **C** in Table 3-1 (in CH_2Cl_2), and the polymerization was complete within 30 min even at the lower initial monomer concentrations (runs 66-67). The resultant polymers, poly(**1**), possessed narrow molecular weight distributions in all cases (M_w/M_n = 1.11-1.19), and the M_n values were very close to those calculated based on the monomer/Mo molar ratios, indicating that the present polymerization took place in a living manner with quantitative initiation as previously communicated.[1] Incomplete polymerization effected with **B** under the same conditions (conversion 33 % by ^{1}H NMR, run 68), indicate that **A** is more efficient initiator than **B** for this polymerization. Reaction of **2** with **A** was complete within 60 min even at low initial monomer concentrations (runs 70-73), whereas the polymerization using both **B** and **C** was not

complete under the same conditions (runs 74-75). These results also clearly indicate that **A** is more efficient initiator than **B**, **C** for the present polymerization.

Table 3-3 summarizes results concerning time course dependences for polymerizations of norbornenes containing glucose (**1**) and maltose (**2**) residues initiated by the molybdenum (**A**) or by the ruthenium (**B**) complex in toluene.[25] As shown in Figure 3-3,[21] the first order rate plots between the propagation rates and the monomer concentrations were observed in all cases. Therefore, the rate constants for polymerization by **A** in toluene are estimated as follows: $k_{\mathbf{1}(\mathbf{A},\text{toluene})} = 1.5\times10^{-1}$ min^{-1} and $k_{\mathbf{2}(\mathbf{A},\text{toluene})} = 6.5\times10^{-2}$ min^{-1}. The rate constants at 25 ºC with **B** could also be estimated in the same manner [$k_{\mathbf{1}(\mathbf{B},\text{toluene})} = 3.0\times10^{-3}$ min^{-1}, $k_{\mathbf{2}(\mathbf{B},\text{toluene})} = 1.2\times10^{-3}$ min^{-1}], and these values are slightly smaller than those when **A** is used as well as those estimated in CH_2Cl_2 [$k_{\mathbf{1}(\mathbf{B},\text{CH2Cl2})} = 8.6\times10^{-3}$ min^{-1}, $k_{\mathbf{2}(\mathbf{B},\text{CH2Cl2})} = 2.5\times10^{-3}$ min^{-1}, based on results in Table 3-1 and Figure 3-2].[25]

Table 3-2. ROMP of monomers **1-2** initiated with **A**, **B** or **C** in toluene at 25 ºC.[a]

Run No.	Monomer	Initiator	$[M]_0$[b] $\times 10^{-2}$	Time / min	M_n[c] (GPC) $\times 10^{-4}$	M_w/M_n[c] (GPC)	Conv.[d] (^{1}H-NMR) /%	Yield[e] / %
63	**1**	**A**	10.7	15	1.17	1.11		92
64	**1**	**A**	3.57	15	1.06	1.13		90
65	**1**	**A**	1.78	15	0.97	1.14		(80)[f]
66	**1**	**A**	1.78	30	1.09	1.18	>97	90
67	**1**	**A**	0.89	30	1.14	1.19	>97	90
68	**1**	**B**	1.78	30	0.39	1.15	33	---[f]
69	**1**	**C**	1.78	30	4.02	1.56	96	>95
70	**2**	**A**	6.60	60	1.24	1.19		90
71	**2**	**A**	2.20	60	1.36	1.11		90
72	**2**	**A**	1.10	60	1.45	1.15	>97	>95
73	**2**	**A**	0.55	60	1.47	1.13		>95
74	**2**	**B**	1.10	60	0.40	1.18	26	---[f]
75	**2**	**C**	1.10	60	2.69	1.27	89	---[f]

[a] Conditions : toluene 1.0 (runs 63, 70), 3.0 (runs 64, 71), 6.0 (runs 65-66, 68-69, 72, 74-75) 12.0 (runs 67, 73) mL, 25 ºC, Mo or Ru 5.35 μmol (for **1**, runs 63-69) or 3.30 μmol (for **2**, runs 70-75), monomer/Ru = 20 (molar ratio), M_n (calculated based on the molar ratio) = 9500 (for **1**) or 1.53×10^4 (for **2**); [b] Initial monomer concentration mmol/mL; [c] GPC data in THF vs polystyrene standard; [d] Conversion estimated by ^{1}H NMR; [e] Isolated yield; [f] The polymerization did not complete, and the yields were based on a mixture of the monomer and polymer.

Table 3-3. ROMP of monomers **1**-**2** initiated with **A** or **B** in toluene.[a]

Run No.	Monomer	Initiator	Time / min	M_n[b] (GPC) $\times 10^{-4}$	M_w/M_n[b] (GPC)	Conv.[c] (^{1}H-NMR) /%	Yield[d] / %
76	**1**	**A**	5	0.55	1.11	55	--[e]
77	**1**	**A**	10	0.82	1.16	72	--[e]
65	**1**	**A**	15	0.97	1.14		(80)[e]
66	**1**	**A**	30	1.09	1.18	>97	90
68	**1**	**B**	30	0.39	1.15	33	---[e]
78	**1**	**B**	60	0.46	1.17	43	---[e]
79	**1**	**B**	120	0.56	1.19	50	---[e]
80	**1**	**B**	240	0.72	1.17	68	---[e]
81	**2**	**A**	15	0.68	1.17	45	--[e]
82	**2**	**A**	30	0.93	1.15	62	--[e]
72	**2**	**A**	60	1.45	1.15	>97	>95
83	**2**	**B**	30	0.35	1.19	22	---[e]
74	**2**	**B**	60	0.40	1.18	26	---[e]
84	**2**	**B**	120	0.45	1.19	30	---[e]
85	**2**	**B**	360	0.71	1.17	47	---[e]

[a] Conditions: toluene 6.0 mL, Mo or Ru 5.35 μmol (for **1**, runs 65-66, 68 76-80) or 3.30 μmol (for **2**, runs 72, 74, 81-85), monomer/Ru = 20 (molar ratio), M_n (calculated based on the molar ratio) = 9500 (for **1**) or 1.53×10^4 (for **2**), respectively, 25 ºC; [b] GPC data in THF vs polystyrene standard; [c] Conversion estimated by ^{1}H NMR; [d] Isolated yield; [e] Incomplete polymerization.

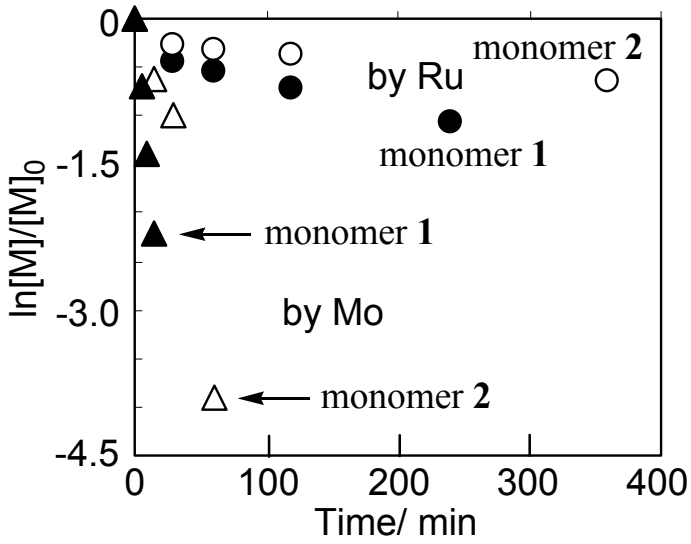


Figure 3-3. Time-course plots vs ln[M]/[M]$_0$ for the polymerization of **1**-**2** with **A** (▲or △) or with **B** (●or ○) in toluene at 25 ºC (molar ratio of monomer/Ru or Mo = 20) based on results shown in Table 3-3. The initial monomer concentration, [M]$_0$: 1.78×10^{-2} (monomer **1**, ▲or ●), 1.10×10^{-2} (monomer **2**, △or ○) mmol/mL, respectively.

3-3-2. Time Course and Monomer Concentration Dependences for the ROMP with Mo(N-2,6-^{i}Pr$_2$C$_6$H$_3$)(CHCMe$_2$Ph)(O^{t}Bu)$_2$ (A), Ru(CHPh)(Cl)$_2$(PCy$_3$)$_2$ (B), and Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$) (C) Initiators using NMR Analysis

*ROMP of **1**-**2** with **B** in $CDCl_3$*

Figure 3-4 shows time-course plots for the polymerization of **1** with **B** in $CDCl_3$ monitored by ^{1}H NMR measurements (integration ratio of olefinic resonances vs acetyl group), and polymerization in toluene-d_8 was also examined for comparison. The polymerization in $CDCl_3$ (marked with ●) took place more efficiently than in toluene-d_8 (marked with +) under the same conditions (the initial monomer concentration 1.07×10^{-1} mmol/mL). Based on the time-course plots vs ln[M]/[M]$_0$ shown in Figure 3-5 (calculated based on Figure 3-4), the rate constants, k values, at 25 ºC were estimated as follows: $k_{\mathbf{1}(\mathbf{B},CDCl3)} = 3.8\times10^{-2}$ min^{-1}, $k_{\mathbf{1}(\mathbf{B},toluene)} = 3.0\times10^{-3}$ min^{-1}. The estimated k values in toluene-d_8 [shown in Figure 3-5 (b)] were the same as those in toluene (shown in Figure 3-3), and this indicates that the result was reproducible irrespective of methods employed (calculated conversion based on the M_n value determined by

GPC or based on the integration ratio of the olefinic resonances in the ^{1}H NMR spectra). In addition, the gradient was independent of the initial monomer concentrations [the observed $k_{\mathbf{1}(\mathbf{B},CDCl3)}$ values were 3.83×10^{-2} min^{-1} (marked with ●), and 3.68×10^{-2} min^{-1} (marked with ■) at the initial concentration of 1.07×10^{-1}, 3.57×10^{-2} mmol/mL, respectively], and the k value observed in $CDCl_3$ is the largest among these conditions employed (CH_2Cl_2, toluene, $CDCl_3$).

Polymerization of **2** in $CDCl_3$ using the ruthenium initiator (**B**) was also monitored by ^{1}H NMR spectra [Figure 3-6 (a), time course plots vs the monomer conversion], and the time-course plots vs ln[M]/[M]$_0$ [calculated based on the conversion, Figure 3-6 (b)] showed a first order dependence between the rate and the monomer concentration, and the slope was independent of the starting monomer concentrations. The k value estimated from these results is 1.3×10^{-2} min^{-1}, which is smaller than that for polymerization of **1** but still larger than that for **2** in CH_2Cl_2.

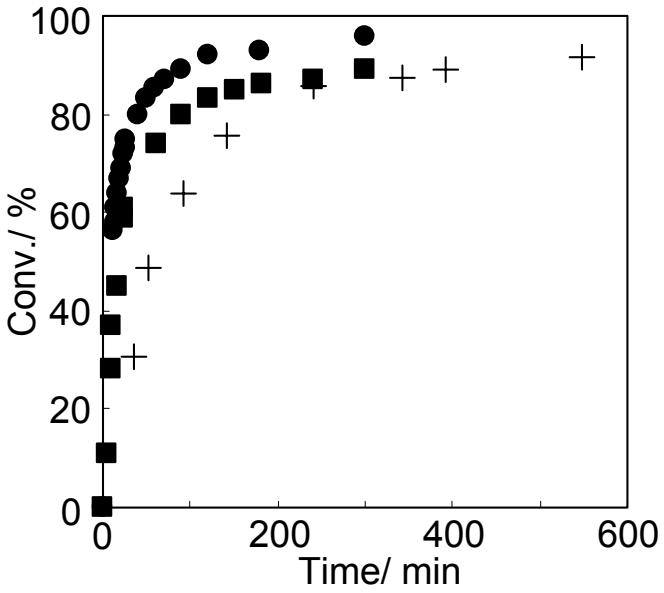


Figure 3-4. Time-course plots vs the monomer conversion for the polymerization of **1** with **B** in toluene-d_8 (+) or in $CDCl_3$ (●, ■) monitored by ^{1}H NMR spectra (monomer/Ru molar ratio = 20). Initial monomer concentration: 1.07×10^{-1} (●, +), 3.57×10^{-2} (■) mmol/mL, respectively.

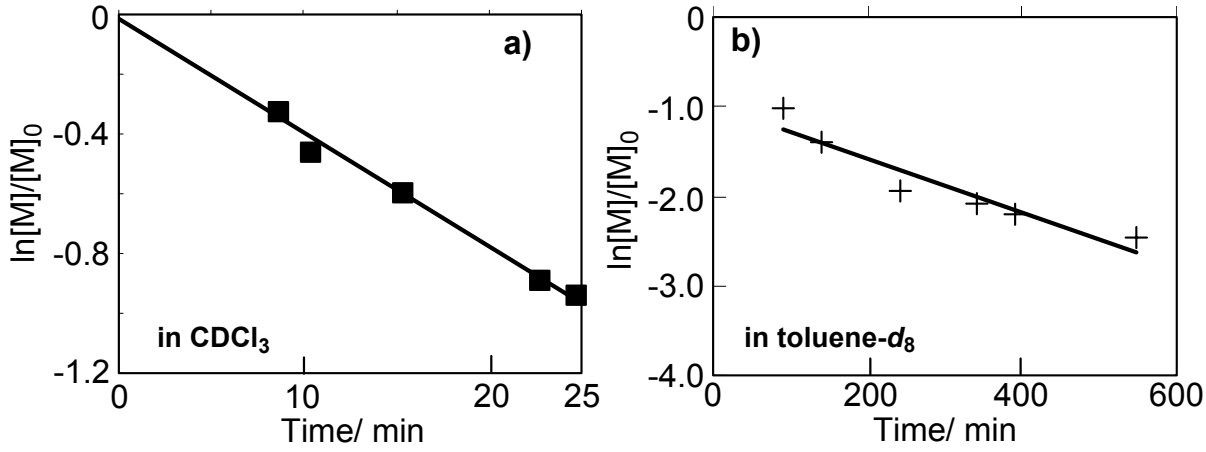


Figure 3-5. Time-course plots vs $\ln[M]/[M]_0$ for the polymerization of **1** with **B** a) in $CDCl_3$ (■) or b) in toluene-d_8 (+) at 25 ºC (molar ratio of monomer/Ru = 20) based on results shown in Figure 3-4. Initial monomer concentration, $[M]_0$: 1.07×10^{-1} (+), 3.57×10^{-2} (■) mmol/mL, respectively.

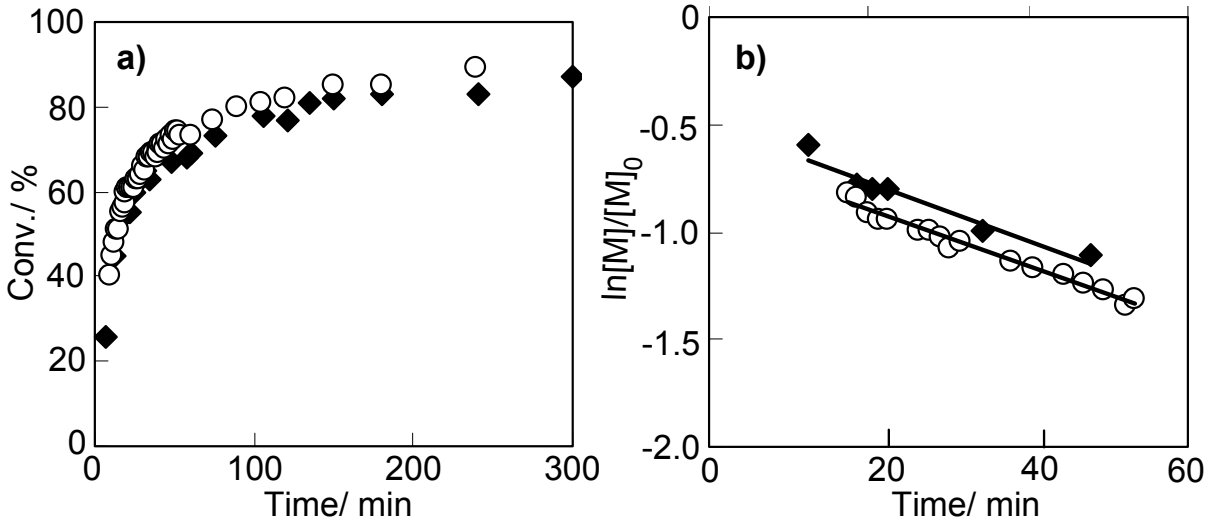


Figure 3-6. Time-course plots vs (a) monomer conversion and (b) $\ln[M]/[M]_0$ for the polymerization of **2** with **B** in $CDCl_3$ at 25 ºC monitored with ^1H NMR spectra (monomer/Ru molar ratio = 20). The initial monomer concentration, $[M]_0$: 6.60×10^{-2} (○), 2.20×10^{-2} (◆) mmol/mL, respectively.

*ROMP of **1-2** with **C***

Figure 3-7 (a) shows time-course plots (vs monomer conversion) for polymerization of **1-2** with the ruthenium initiator (**C**) monitored by ^{1}H NMR measurement,[18-20] and these polymerizations took place rather more rapidly than those using **B** under the same initial monomer concentrations.[26] First order dependences were obtained between the monomer consumption rates and the monomer concentrations in all cases [Figure 3-7 (b)], and the slope was independent of the starting monomer concentrations in all cases.[19,20] Based on the results shown in Figure 3-7 (b), time-course plots vs $\ln[M]/[M]_0$, the rate constants, k values (at 25 ºC), for the polymerization of **1-2** using initiator **C** were estimated as follows: $k_{\mathbf{1}(\mathbf{C},CDCl3)} = 6.7\times10^{-2}$ min^{-1}, $k_{\mathbf{2}(\mathbf{C},CDCl3)} = 5.9\times10^{-2}$ min^{-1}, respectively. It is interesting to note that the observed values (as well as the monomer consumption time courses) were not strongly dependent upon monomer employed (**1** or **2**) whereas the values obtained from the corresponding reaction effected with **A** and **B** were dependent upon the monomer employed.

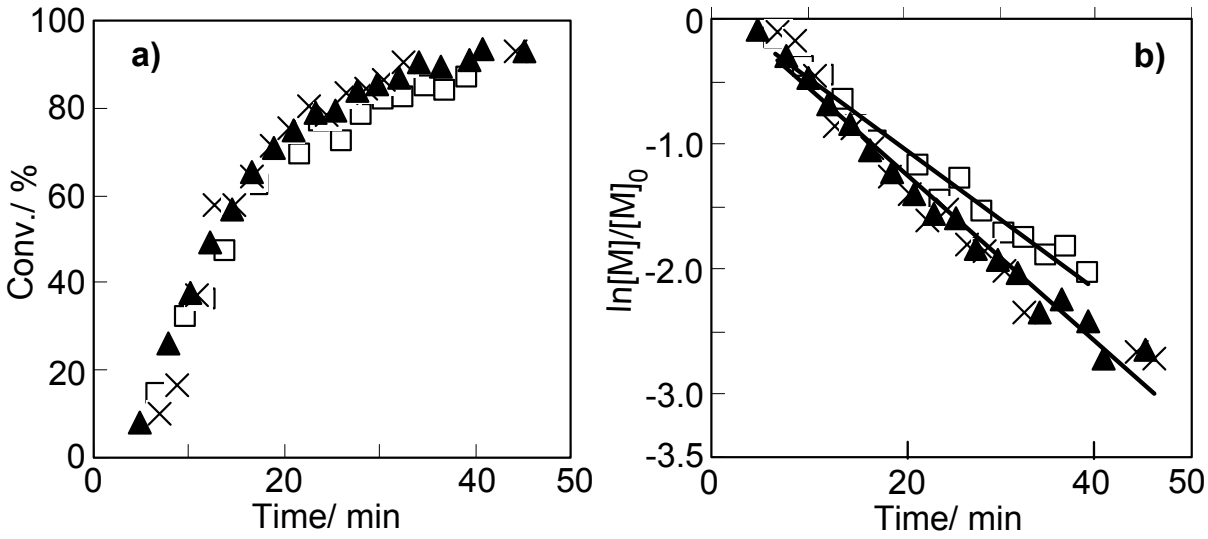


Figure 3-7. Time-course plots vs (a) monomer conversion and (b) $\ln[M]/[M]_0$ for the polymerization of **1-2** with **C** in $CDCl_3$ at 25 °C monitored with ^{1}H NMR spectra (monomer/Ru molar ratio = 20). The initial monomer concentration, $[M]_0$: 1.07×10^{-1} (▲), 3.57×10^{-2} (×) mmol/mL (monomer **1**), or 2.20×10^{-2} (□) mmol/mL (monomer **2**), respectively.

3-3-3. Evaluation of the Rate Constants for the ROMP with Mo(N-2,6-$^{i}Pr_2C_6H_3$)(CHCMe$_2$Ph)(O^{t}Bu)$_2$ (A), Ru(CHPh)(Cl)$_2$(PCy$_3$)$_2$ (B), and Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$) (C) Initiators (at 25 ºC)

Table 3-4 summarizes observed k values (rate constants) for the polymerization of **1** and **2** by the molybdenum (**A**), and ruthenium (**B** and **C**) initiators in various solvents (toluene, CH_2Cl_2, and $CDCl_3$) at 25 ºC. Based on these results as well as those shown in Tables 3-2 and 3-3, it is concluded that ROMP with **A** is more suited than with **B** or **C** to prepare polymers efficiently in a precise manner.[27] In addition, it is clear that the observed k value increased in the order, **A** > **C** > **B**, and a strong solvent effect was observed in particular for polymerizations using the ruthenium initiator **B** [$k_{\mathbf{1}(\mathbf{B}CDCl3)} > k_{\mathbf{1}(\mathbf{B}CH2Cl2)} > k_{\mathbf{1}(\mathbf{B}toluene)}$].[24] The k value for the polymerization of **2** with **C** in $CDCl_3$ was similar to the corresponding reaction with **A** in toluene [$k_{\mathbf{2}(\mathbf{A}toluene)} = 6.5\times10^{-2}$ vs $k_{\mathbf{2}(\mathbf{C}CDCl3)} = 5.9\times10^{-2}$], although the polymerization with **C** did not proceed in a living manner. Since a comparison of the performance of these initiators under the same conditions particularly for ROMP has been limited, these results should be important especially for the synthesis of desired ROMP polymers as well as for designing more efficient metathesis initiators.[28] We are currently investigating the possibility of preparing poly(macromonomer)s containing sugars by the repetitive ROMP technique,[29] and in addition are evaluating the carbohydrate functionalized polymers for their specific interaction with carbohydrate-binding proteins (lectins).[28]

Table 3-4. Summary of the kinetic data for the ROMP of monomers **1-2** with Mo(CHCMe$_2$Ph)(N-2,6-^{i}Pr$_2$C$_6$H$_3$)(O^{t}Bu)$_2$ (**A**), Ru(CHPh)(Cl)$_2$(PCy$_3$)$_2$ (**B**), or Ru(CHPh)(Cl)$_2$(IMesH$_2$)(PCy$_3$) (**C**).

Monomer	Initiator	Solvent	k_{obs} (min^{-1})	Analysis
1	**A**	toluene	1.5×10^{-1}	Figure 3-3
1	**B**	toluene	3.0×10^{-3}	Figure 3-3
1	**B**	toluene-d_8	3.0×10^{-3}	Figure 3-5
1	**B**	CH_2Cl_2	8.6×10^{-3}	Figure 3-2
1	**B**	$CDCl_3$	3.8×10^{-2}	Figure 3-5
1	**C**	$CDCl_3$	6.7×10^{-2}	Figure 3-7
2	**A**	toluene	6.5×10^{-2}	Figure 3-3
2	**B**	toluene	1.2×10^{-3}	Figure 3-3
2	**B**	CH_2Cl_2	2.5×10^{-3}	Figure 3-2
2	**B**	$CDCl_3$	1.3×10^{-2}	Figure 3-6
2	**C**	$CDCl_3$	5.9×10^{-2}	Figure 3-7

3-4. References and Notes

1. Nomura, K.; Schrock, R. R. *Macromolecules* **1996**, *29*, 540-545.
2. Nomura, K.; Sakai, I.; Imanishi, Y.; Fujiki, M.; Miyamoto, Y. *Macromol. Rapid Commun.* **2004**, *25*, 571-576.
3. Some of these results were presented at the *15th International Symposium on Olefin Metathesis and Related Chemistry* (Kyoto, Japan, Aug, 2003; paper 06).
4. Kiessling, L. L.; Strong, L. E. In *Alkene Metathesis in Organic Synthesis*; Fürstner, A. Ed.; Springer-Verlag: Berlin, 1998; pp199-231. Typical reports for synthesis of carbohydrate-based (neobio) polymers are cited therein.
5. Kiessling, L. L.; Owen, R. M. In *Handbook of Metathesis*: Grubbs R. H. Ed.; Wiley-VCH: Weinheim, 2003; Vol. 3, pp180-225.
6. Mortell, K. H.; Gingas, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **1994**, *116*, 12053-12054.
7. Mortell, K. H.; Weatherman, R. V.; Kiessling, L. L. *J. Am. Chem. Soc.* **1996**, *118*, 2297-2298.
8. Manning, D. D.; Strong, L. E.; Hu, X.; Beck, P. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 3161-3162.
9. Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931-9932.
10. Gordon, E. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30-31.
11. Cairo, C. W.; Gestwicki, J. E.; Kanai, M.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 1615-1619.
12. Gestwicki, J. E.; Cairo, C. W.; Strong, L. E.; Oetjen, K. A.; Kiessling, L. L. *J. Am. Chem. Soc.* **2002**, *124*, 14922-14933.
13. Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248-7255.
14. Iyer, S.; Rele, S.; Grasa, G.; Nolan, S.; Chaikof, E. L. *Chem. Commun.* **2003**, 1518-1519. In this paper, the molecular weight distribution (M_w/M_n) of a hyaluronan neoglycopolymer prepared with ($IMesH_2$)(Cy_3P)$RuCl_2$(CHPh) (**C**) was 1.17 and the average degree of the monomer repeating unit estimated by ^{1}H NMR was 15.5 (the initial molar ratio of the monomer/Ru was 20).

15. Gibson, V. C.; Marshall, E. L.; North, M.; Robson, D. A.; Williams, P. J. *Chem. Commun.* **1997**, 1095-1096.
16. North, M. In *Ring-Opening Metathesis Polymerisation and Related Chemistry*; Khosravi, E.; Szymanska-Buzar, T., Eds.; Kluwer: Dordrecht, 2002; pp 157-166 and pp 167-176.
17. As described by Kiessling in ref. 6 (as unpublished results), the molecular weight distributions for an acetylated polymer[10] with a degree of polymerization 10 were less than or equal to 1.2, and the polymers with a degree of polymerization greater than 50 could not be generated under these conditions.
18. Bielawski, C. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2903–2906.
19. Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.
20. Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103-10109.
21. The monomer concentrations at each reaction time were calculated on the basis of the conversion of the monomers, and the ratios of the M_n values (measured by GPC) against the values after the complete consumption of the monomer were chosen for the calculation of the conversion. Although it was possible to use the calculated values based on the ^{1}H NMR spectra (protons in olefinic resonances), and they were in good agreement with those calculated based on GPC (M_n values), the calculation based on the ^{1}H NMR spectra was somewhat difficult, particularly in low-monomer conversion regions, which were especially important for the estimation of the rate constant.
22. Although the monomers were a mixture of endo and exo isomers (endo/exo = 87/13) and the endo monomers often took longer to polymerize than the exo isomers, probably because of the unfavorable steric interaction between the monomers and the initiating species,[15-17] as described previously, first-order relationships were observed between the propagation rate and the monomer concentration. This was probably due to the concentration of the exo isomers being rather low (13%) in this case, and the observed rate constants were, therefore, the values for the consumption of the endo isomers.

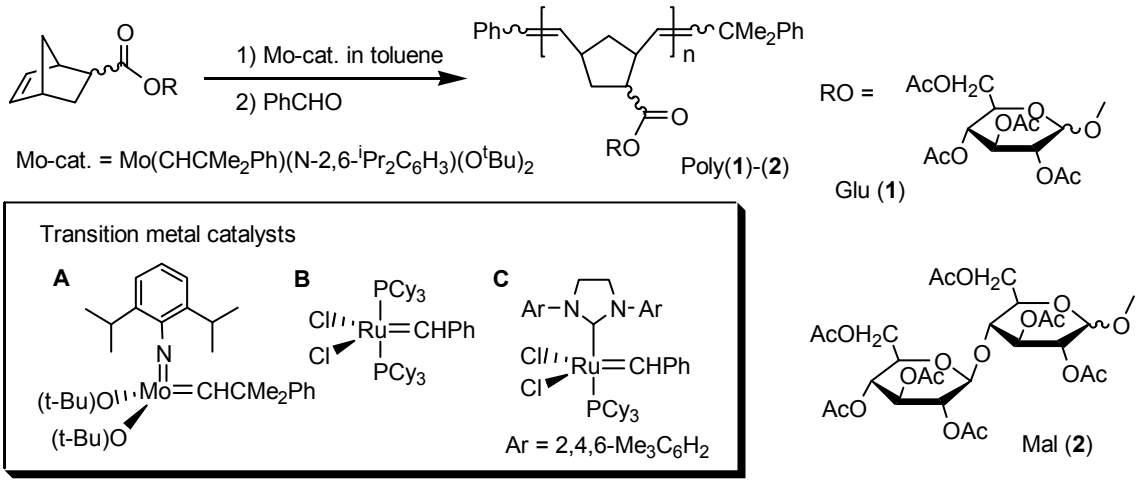
23. Because a first-order dependence between the propagation rates and the monomer concentration was observed, rate constant *k* can be calculated with the following equation: $-d[M]/dt = k[M]$ and $-\ln[M]/[M]_0 = -kt$, where $[M]_0$ is the initial monomer concentration and [M] and *t* are the concentration at each period and the time, respectively. The expression $k_{\mathbf{1}(\mathbf{B}CH2Cl2)}$ [where **1** is monomer **1**, **B** is initiator **B**, and CH_2Cl_2 is solvent CH_2Cl_2] was used for clarity in this study.
24. Although the polymerizations in CH_2Cl_2 with molybdenum initiator **A** were also explored, a partial decomposition of the initiator, especially at low monomer concentrations, was observed. Because the propagation rate in toluene was rather slow in comparison with that in CH_2Cl_2, and because the polymerization also took place without the decomposition, the kinetic estimation was performed in toluene, as discussed in this article.
25. Polymerizations of **1**-**2** effected with ruthenium initiator **C** were also attempted, but the resultant polymers possessed bimodal molecular weight distributions, and the results (the ratio of high-molecular-weight peaks to low-molecular-weight peaks) were not reproducible. Therefore, we estimated rate constant *k* with ^{1}H NMR time-course measurements as the consumption rate of monomers.
26. In fact, polymerizations of **1** and **2** by **C** in toluene-*d*8 were attempted to monitor the time course by ^{1}H NMR spectra. However, the results were not reproducible, especially in toluene. This may be due to the slow initiation by **C**, especially in toluene, although it is still not clear why it was difficult to reproduce the time course in this polymerization.
27. Although we know that the molybdenum-F_6 initiator, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}{}^iPr_2C_6H_3)[OCMe(CF_3)_2]_2$, should be more a efficient initiator than **A**, we chose F_o initiator in this case. This is because, as described in ref. 2, it appears to be the mildest of the initiators, especially for ROMP, and because we wanted to compare our previous results with molybdenum (introduced in that article) with ruthenium initiators.
28. Because the acetyl group in the sugar residue in poly(**1**)-(**2**) can be deprotected smoothly by an established procedure (K_2CO_3 in MeOH), it is possible to evaluate the interactions

of these polymers with carbohydrate-binding proteins (Lectins), such as Concanavalin A. These results will be reported in a forthcoming article.

29. Nomura, K.; Takahashi, S.; Imanishi, Y. *Macromolecules* **2001**, *34*, 4712-4723.

Concluding Remarks

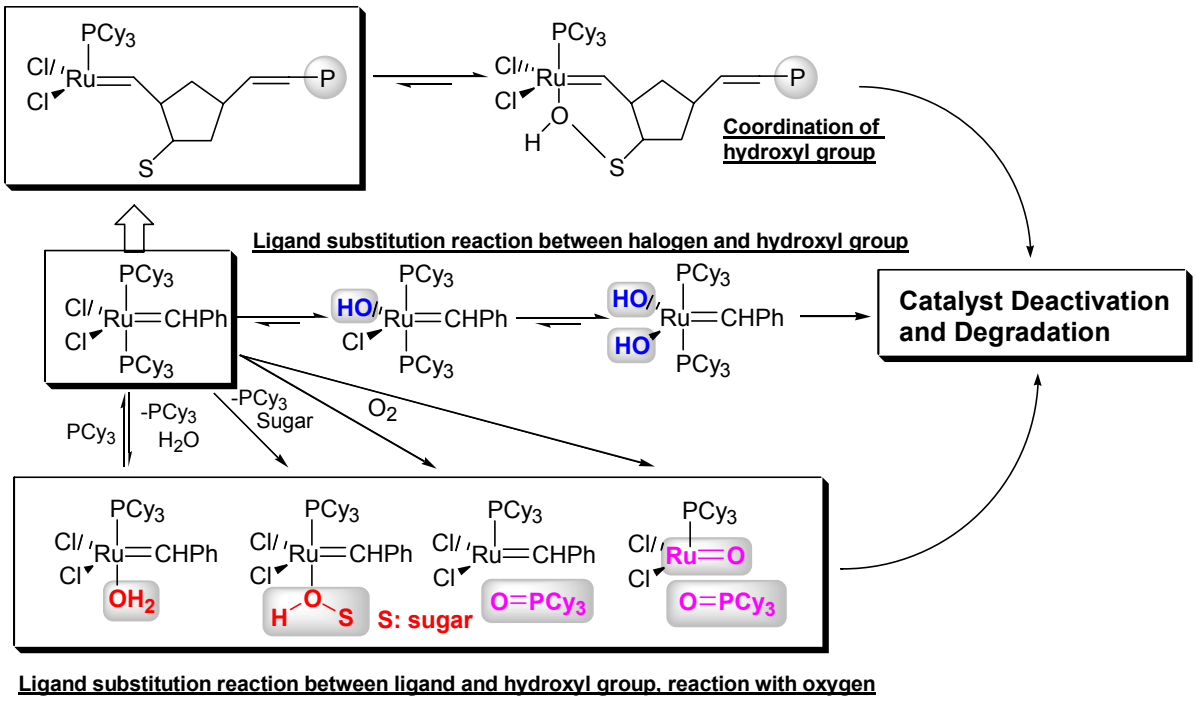
This thesis discloses a development of new synthetic methods using transition metal catalysts, in particular, the ring-opening metathesis polymerization (ROMP) of norbornenes containing acetyl-protected carbohydrates e.g. glucose, [monosaccharide; i.e., 2,3,4,6-tetra-*O*-acetyl-glucos-1-*O*-yl 5-norbornene-2-carboxylate (**1**)], or maltose, [disaccharide; i.e., 2,3,6,2',3',4',6'-hepta-*O*-acetyl-maltos-1-*O*-yl 5-norbornene-2-carboxylate (**2**)], using the well-defined molybdenum-alkylidene initiator, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}^{i}Pr_2C_6H_3)(O^{t}Bu)_2$ (**A**), and ruthenium initiators, $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**; Cy = cyclohexyl) and $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**; $IMesH_2$ = 1,3-dimesityl-4,5-dihydromidazol-2-ylidene) (Scheme 1).



Scheme 1

In our previous reports, we proved that the ROMP of norbornenes containing acetyl-protected carbohydrates with a molybdenum initiator under controlled conditions, (highly purified monomers, anhydrous solvents, and a nitrogen atmosphere), took place in a living fashion. In contrast, the synthesis of carbohydrate ROMP polymers with ruthenium initiators did not take place in a living fashion in the previous reports. For this reason, we assumed that

the ruthenium catalysts include several side reactions (e.g. with the hydroxyl group of carbohydrate, water, and oxygen) (Scheme 2), and the deactivation and degradation of the ruthenium initiator are thus caused by these reactions (e.g. a ligand substitution reaction between halogen and hydroxyl group). In order to control catalyst deactivation and degradation, we tried the ROMP of norbornenes containing acetyl-protected carbohydrate under the same conditions with molybdenum initiators.



Scheme 2

In chapter 2, the polymerizations of **1-2** with initiator **B** were performed by varying monomer/Ru molar ratios (= 10-40). Through this research, we found that the polymerizations completed in all cases, and the resultant polymers possessed narrow molecular weight distributions (M_w/M_n = 1.04-1.17). The M_n values for the resultant polymers increased upon increasing monomer/Ru molar ratios, and the M_n values were close to those calculated based on monomer/Ru molar ratios. It is therefore suggested that the present polymerization proceeds in a living fashion with high initiation efficiency. In order to provide evidence that the ROMP with initiator **B** was living, in particular to confirm the polymer-chain end is still living after

consumption of monomer, post polymerizations were conducted after the consumption of the first monomer. Multiblock copolymers consisting of **1** and **2** could be prepared by adding monomers sequentially after consumption of the former monomer (from the homopolymer to the tetra-block copolymer), and the molecular weight distributions for the resultant copolymers were narrow in all cases (M_w/M_n = 1.13-1.19). These results clearly indicate that the catalyst deactivation was not seen during the polymerization of norbornenes containing acetyl-protected carbohydrates under these highly controlled (*perfectly* anhydrous under inert atmosphere) conditions.

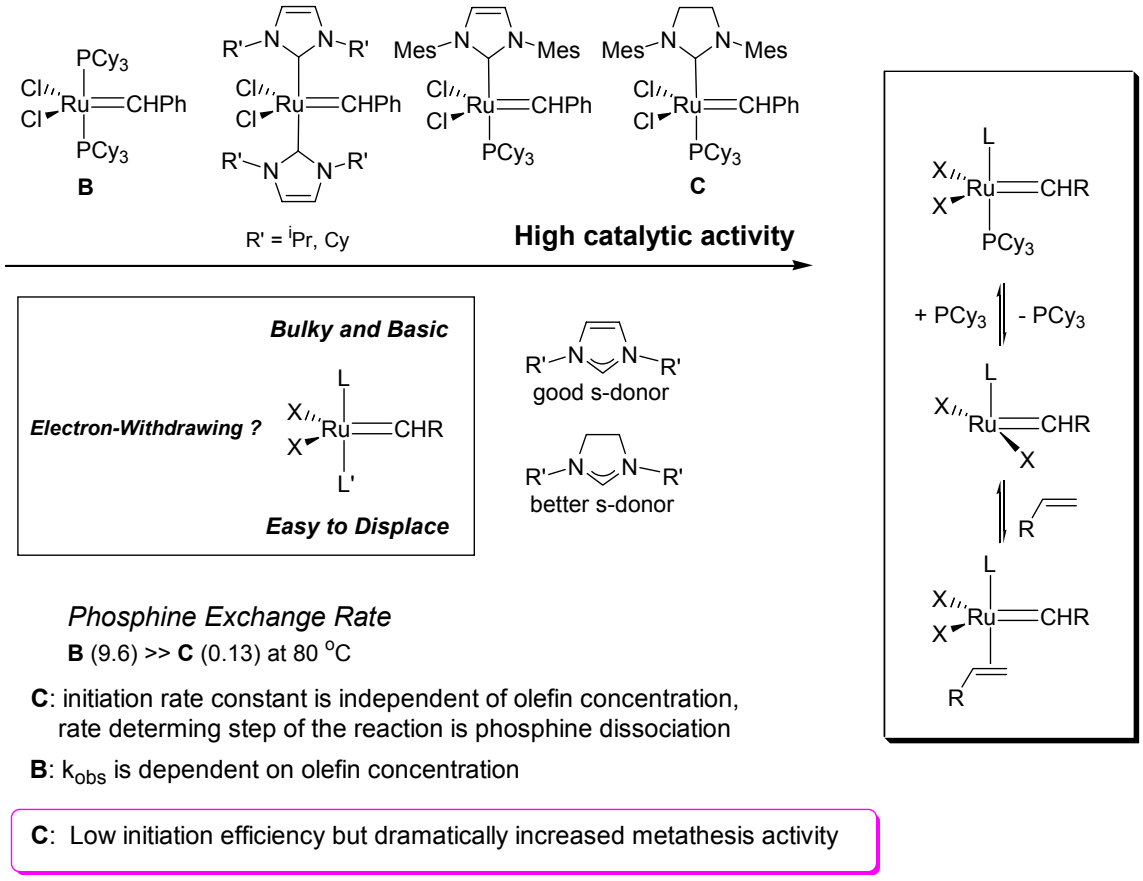
ROMP of **1-2** with initiator **C** were performed by varying the monomer/Ru molar ratios, and the resultant polymers possessed higher M_n values than those based on the monomer/Ru molar ratios and the molecular weight distributions were somewhat broad (M_w/M_n = 1.49-1.95), whereas the M_n values obtained by initiator **B** were almost identical to the calculated values based on monomer/Ru molar ratio with narrow distributions. It should be noted that the polymerization with initiator **C** is not affected by monomer concentration and polymerization time. In fact, the polymerization with 1000 equivalent of **1** completed after 1 h. However, the ROMP by initiator **C** did not take place in a living fashion. In addition, we believed that initiator **C** reacts with carbon-carbon double bonds, in both the cyclic monomer and also in the principal polymer main chain.

Using this technique under these highly controlled (*perfectly* anhydrous under inert atmosphere) conditions without unprotected carbohydrate hydroxyl groups, carbohydrate ROMP polymers with precise control of the molecular weight, chain length of carbohydrate ROMP polymers with high molecular weight were synthesized by ruthenium initiators (**B**, and **C**).

In chapter 3, the differences in the performances of these initiators (**A**, **B**, and **C**) were examined from the *k* values (rate constants) of the ROMP. Since first order relationships between the propagation rate and the monomer concentration were observed in all polymerization runs, we were able to estimate the *k* values (rate constants) for the

polymerization of **1** and **2** by the molybdenum (**A**), ruthenium (**B**, and **C**) initiators in various solvents (toluene, CH_2Cl_2, $CDCl_3$) at 25 ºC. From the comparison of resulting initiator performance, the observed k value increased in the order: **A** > **C** > **B**, and the effect of the steric bulk of the monomer was observed especially for the polymerization (**B** > **A** > **C**). These results depend above all, on the properties and the ROMP mechanism of the catalysts (Scheme 3). In the case of the molybdenum catalyst **A**, the ROMP proceeds in a living fashion with high initiation efficiency, attaching directly to the carbon-carbon double bonds of the monomeric olefins (via the metal-carbene complexes). The ROMP by ruthenium catalyst **B** indicates a similar tendency. In particular, the dissociations of phosphine in the catalyst **B** have an effect on the initiation of ROMP. Therefore, initiator **A** is more useful for ROMP than initiator **B**. In contrast, ROMP by the ruthenium catalyst **C** proceeds with a rapid propagation vs. a slow initiation, especially in comparison with ruthenium catalyst **B**. The difference of reactivity with ruthenium catalysts (**B**, and **C**) is implicated by the dissociation rates of the phosphine. To ligand substituting a PCy_3 ligand for a highly bulky and basic ligand in ruthenium catalyst **B**, ROMP using the new ruthenium catalyst **C** indicates a high reactivity for cyclic olefins, there was not effect of steric bulk of monomer, and the resultant carbohydrate ROMP polymers possessed broad molecular weight distributions, with high molecular weights.

In addition, strong solvent effects were observed, especially for the polymerization with initiator **B** [$CDCl_3$ > CH_2Cl_2 > toluene]. The k value for polymerization of **2** by initiator **C** in $CDCl_3$ was similar to that by initiator **A** in toluene, although the polymerization by initiator **C** did not proceed in a living manner. Based on these results, the ROMP by initiator **A** is more suited than that by initiator **B** or **C** to prepare polymers efficiently in a precise manner.



Scheme 3

In this thesis (chapter 2, 3), the precise synthesis of carbohydrate polymers by ROMP can be demonstrated using the well-defined molybdenum-alkylidene initiator, $Mo(CHCMe_2Ph)(N\text{-}2,6\text{-}^{i}Pr_2C_6H_3)(O^{t}Bu)_2$ (**A**), and ruthenium initiators, $Ru(CHPh)(Cl)_2(PCy_3)_2$ (**B**; Cy = cyclohexyl) and $Ru(CHPh)(Cl)_2(IMesH_2)(PCy_3)$ (**C**; $IMesH_2$ = 1,3-dimesityl-4,5-dihydromidazol-2-ylidene). The ruthenium catalysts are more suitable for their practical use than the molybdenum catalysts (availablity, ease of synthesis, and functional group tolerance), and these results are reflected by their wide use in the fields of both organic and polymer chemistry.

List of Publication

I. Academic journals

"Synthesis of homopolymers and multiblock copolymers by the living ring-opening metathesis polymerization of norbornenes containing acetyl-protected carbohydrates with well-defined ruthenium and molybdenum initiators"

Y. Miyamoto, M. Fujiki, and K. Nomura

J. Polym. Sci., Part A: Polym. Chem., **42,** 4248-4265 (2004).

Other publications described in this thesis

"Living ring-opening metathesis polymerization of norbornenes containing acetyl-protected carbohydrates using well-defined molybdenum and ruthenium initiators"

K. Nomura, I. Sakai, Y. Imanishi, M. Fujiki, and Y. Miyamoto

Macromol. Rapid Commun., **25**, 571-576 (2004).

Other publications not described in this thesis

[1] "In vitro evolution and characterization of a ligase ribozyme adapted to acidic conditions: Effect of further rounds of evolution"

Y. Miyamoto, N. Teramoto, Y. Imanishi, and Y. Ito

Biotechnol. Bioeng. in press.

[2] "In vitro adaptation of a ligase ribozyme for activity under a low-pH condition"

Y. Miyamoto, N. Teramoto, Y. Imanishi, and Y. Ito

Biotechnol. Bioeng., **75**(5), 590-596 (2001).

[3] "Epitope-specific impairment of production of antibody against merozoite surface glycoprotein 1 of Plasmodium falciparum in symptomatic patients with malaria"

J. Fu, M. Hato, H. Ohmae, H. Matsuoka, M. Kawabata, K. Tanabe, Y. Miyamoto, J. L. Leafasia, Y. Chinzei, and N. Ohta

Parasitol. Res., **86**(5), 345-351 (2000).

II. International conference proceedings

[1] "Ring-opening metathesis polymerization of norbornenes containing acetyl-protected sugars by well-defined Ru and Mo initiators"

Y. Miyamoto, M. Fujiki, and K. Nomura

40th IUPAC International Symposium on Macromolecules (IUPAC MACRO), poster presentation (Paris, France, July 2004).

[2] "Ring-opening metathesis polymerization of norbornenes containing sugars"

K. Nomura, I. Sakai, M. Fujiki, and Y. Miyamoto

15th International Symposium on Olefin Metathesis and Related Chemistry (ISOMXV), poster presentation (Kyoto, August 2003).

[3] "Precise design and synthesis of "sugar-coated" polymers by living ring-opening metathesis polymerization''

Y. Miyamoto, I. Sakai, M. Naito, K. Nomura, and M. Fujiki

2nd K-JIST/NAIST Joint Symposium on Advanced Materials, poster presentation (Nara, November 2002).

III. Domestic conference

[1] "モリブデンおよびルテニウム錯体触媒を用いる環状オレフィンの開環メタセシス重合による糖鎖置換ポリマーの精密合成"

宮本義孝、坂井一郎、藤木道也、野村琴広

第 33 回石油・石油化学討論会, 大阪国際会議場, 2003 年 11 月 17-19 日.

[2] “Schrock 型モリブデンーアルキリデン錯体を用いるリビング開環メタセシス重合手法を利用した糖鎖置換ポリマーの合成と糖結合タンパク質との特異的な相互作用

坂井一郎、川添直樹、宮本義孝、野村琴広

第 49 回有機金属化学討論会，神戸大学，2002 年 9 月 12-13 日.

Other publications not described in this thesis

[1] “特殊環境下で触媒作用を示すリボザイムの進化分子工学による創成’’

宮本義孝、寺本直純、伊藤嘉浩、今西幸男

第 49 回高分子学会年次大会, 名古屋国際会議場, 2000 年 5 月 29-31 日.

[2] “特殊環境下で触媒作用を示すリボザイムの進化分子工学による創成’’

宮本義孝、寺本直純、伊藤嘉浩、今西幸男

第 48 回高分子討論会, 新潟大学, 1999 年 10 月 6-8 日.

[3] “進化分子工学による人工リガーゼリボザイムの創製’’

寺本直純、宮本義孝、伊藤嘉浩、今西幸男

第 1 回日本 RNA ミーティング, 京都, 1999 年 8 月 3-5 日.

[4] “進化分子工学による非生理的条件下で触媒作用を示す高分子の創成’’

宮本義孝、寺本直純、伊藤嘉浩、今西幸男

第 48 回高分子学会年次大会, 国立京都国際会館, 1999 年 5 月 27-29 日.

Acknowledgments

The present research was partly supported by the Young Research Award for Nano-Technology, Research and Education Center for Materials Science, Nara Institute of Science and Technology and was carried out from 2002 to 2003 at the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology.

The author would like to express his sincere gratitude to Professor Michiya Fujiki of the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology, for his constant guidance, encouragement and supervision throughout the course of this research. The author is deeply indebted to Associate Professor Kotohiro Nomura for his constant guidance, insightful opinions, supervision and heartwarming encouragement throughout the course of this research, and for his comments on the presentation of this thesis.

The author wishes to express his sincere gratitude to Emeritus Professor Yukio Imanishi (formerly of the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology), for his constant guidance, encouragement, and instructive comments throughout the course of the previous research (from 1998 to 2001). Sincere gratitude is also due to Professor Yoshihiro Ito of Kanagawa Academy of Science and Technology and Dr. Naozumi Teramoto of the Department of Life and Environmental Sciences, Faculty of Engineering, Chiba Institute of Technology, (formerly of the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology), for his constant guidance, encouragement and instructive comments throughout the course of the previous research.

The author is sincerely grateful to Professor Mikio Kataoka of the Laboratory of Bioenergetics and Biophysics, Graduate School of Materials Science, Nara Institute of Science and Technology, for his valuable discussion and critical reading of this thesis.

The author is sincerely grateful to Professor Masao Tanihara of the Biocompatible Materials Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology, for his valuable discussion and critical reading of this thesis.

The author is sincerely grateful to Associate Professor Ryuichi Shirai of the Functional Synthesis Chemistry Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology, for his instructive comments and valuable suggestions on this research.

The author is sincerely grateful to Dr. Giseop Kwak and Dr. Masanobu Naito of the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology.

The author is sincerely grateful to Mr. Shintaro Saito of the Functional Synthesis Chemistry Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology and Mr. Ichiro Sakai of GENERAL Co., Ltd (formerly of the Advanced Polymer Science Laboratory, Graduate School of Materials Science, Nara Institute of Science and Technology), for his valuable discussion.

The author would like to thank his colleagues in the Fujiki's Laboratory and the Imanishi's Laboratory in Nara Institute of Science and Technology for their encouragement during the course of all research.

Finally, the author really thanks his parents Takao and Sachiko Miyamoto, his sister Manami Miyamoto, and his brother Nobuhiro Miyamoto for their understanding, warm support, and heartfelt encouragement.

December, 2004

Yoshitaka Miyamoto