Control of ring size selectivity by substrate directable RCM†

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Hydroxy groups may exert strong catalyst-directing effects in olefin metathesis reactions, which are exploited for a ring size-selective RCM reaction.

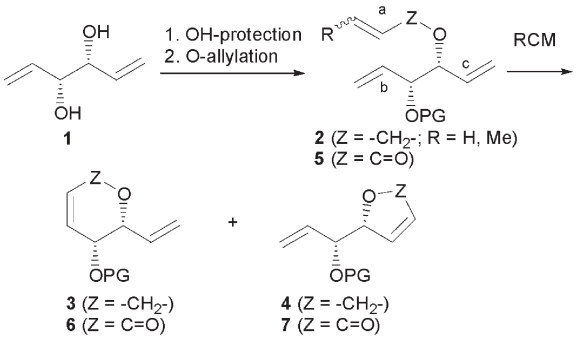
Due to the discovery of modern precatalysts based on molybdenum[1] and ruthenium,[2] ring closing metathesis (RCM) of olefins has become one of the most important methods for the synthesis of carba- and heterocycles.[3] RCM reactions of substrates with more than two double bonds available for metathesis are potentially very useful.[4] If, for instance, trienes are subjected to the conditions of an olefin metathesis reaction, cyclo- or heterocycloalkenes, bearing an additional exocyclic C=C-double bond, result. It has been demonstrated that selective synthetic modification of this exocyclic double bond is possible using established alkene functionalization reactions such as ozonolysis[5] or hydroformylation,[6] and that such strategies might be useful for the synthesis of interesting target molecules. Tetraenes are also interesting substrates for olefin metathesis reactions because they can be converted into bicyclic molecules *via* double ring closing metathesis.[7] Utilization of such concepts for organic synthesis requires the efficient control of various selectivity issues. For instance, the RCM of tri- or tetraenes with two enantiotopic[8] or diastereotopic groups[9] has been described, and can be achieved with moderate to excellent stereoselectivities.[10] Regioselectivity becomes an important issue for tri- or tetraenes if different cyclization modes, leading to different ring sizes, are possible. We came across this selectivity issue in the course of a project directed at the exploitation of D-mannitol-derived dienediol **1** for the metathesis-based synthesis of dihydrofurans and dihydropyrans. Upon selective protection of one hydroxy group of C_2-symmetric **1** and allylation of the remaining hydroxy function, trienes **2** result, which give dihydropyrans **3** *via* "ab"-ring closure, or dihydrofurans **4** *via* "ac"-ring closure. Dienediol **1** has previously been used for the synthesis of acrylates **5**. Quinn *et al.* recently showed that submission of these trienes to RCM conditions results in the exclusive formation of five-membered lactones **7** (Z = C=O),[11] while Michaelis and Blechert demonstrated that a six-membered lactone can be accessed selectively by differentiating the two C=C-double bonds in *ent*-**1** *prior* to the RCM event with a cross metathesis (CM) step.[12] Virolleaud and Piva described related work, where five- and six-membered unsaturated lactones are formed in a 2 : 1 ratio.[13] In the case of acrylates **5**, initiation most likely occurs at C=C-double bonds "b" or "c", while initiation at the electron deficient double bond "a" appears to be very unlikely. We therefore thought that interesting differences must also be expected for allyl ethers **2** (Z = $-CH_2-$, R = H), which will most likely undergo preferred initiation at the sterically least hindered "a"-double bond (Scheme 1). From a practical point of view, it would be desirable to have conditions at hand that will allow the selective synthesis of either dihydropyrans **3** or dihydrofurans **4** from a common precursor **1**. It can be expected that three parameters will have influence on the ring size selectivity:

(a) The protecting group (PG). A directing effect of the PG might be observed for sterically demanding protecting groups or if the PG is a coordinating group that is capable of directing the catalyst selectively to one olefinic moiety.[14] It might also be possible that electron withdrawing protecting groups might exert subtle electronic effects on the closest double bond, thereby influencing the tendency to initiate at this particular site.

(b) The substituent R of the allyl ether group. Increasing the number of substituents at a double bond normally reduces the tendency for initiation at this particular site.[15]

(c) The precatalyst. Remarkable differences have sometimes been observed between first ([$Cl_2(PCy_3)_2Ru$=CHPh], **A**) and second ([$Cl_2(PCy_3)(H_2IMes)Ru$=CHPh], **B**) generation Grubbs' catalysts, not just with respect to reactivity. In certain cases, *qualitative* differences have been observed, *e.g.* different *E*/*Z*-ratios in macrocyclizations and CM reactions,[16] and different diastereomeric ratios in diastereoselective RCM reactions.[17]

We started our investigation with triene **2aa** (PG = Bn, R = H). Using the first generation catalyst **A**, a significant preference for the formation of dihydrofuran **4a** over dihydropyran **3a** (**3a** : **4a** = 1 : 12) was observed (Table 1). The ratio of six- to five-membered rings slightly increased at higher temperature, giving rise to the speculation that the formation of dihydrofurans might be kinetically preferred. This observation is in accord with the previously reported selective formation of five-membered lactones **7** by the RCM of acrylates **5** in the presence of the more active



Scheme 1 Regioselective RCM of mannitol-derived trienes.

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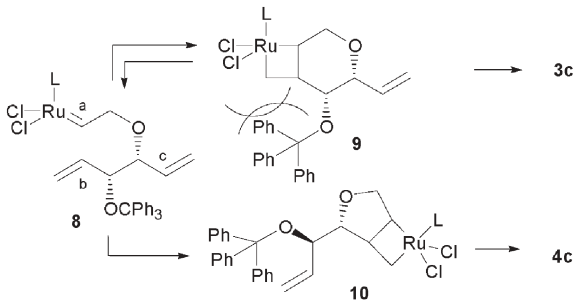
Table 1 Results of the selectivity study

2	PG	R	Catalyst	Conversion (%)[a]	Ratio **3** : **4**[a]	Product (Yield (%))[e]
2aa	Bn	H	**A**	99	1 : 12	**4a** (88)
2aa	Bn	H	**A**	55[b]	1 : 7	—
2aa	Bn	H	**B**	99	1 : 1	—
2aa	Bn	H	**B**	<5[c]	n. d.	—
2aa	Bn	H	**B**	99[b]	1 : 1	—
2ba	TBDMS	H	**A**	99	<1 : 20	**4b** (90)
2ba	TBDMS	H	**B**	99	1 : 2	—
2ca	CPh_3	H	**A**	90	<1 : 20	**4c** (68)
2ca	CPh_3	H	**B**	99	1 : 3	—
2da	CO_2Et	H	**A**	99	1 : 10	**4d** (88)
2da	CO_2Et	H	**B**	99	1 : 1	—
2da	CO_2Et	H	**A**	99[d]	1 : 11	—
2da	CO_2Et	H	**B**	99[d]	1 : 1.3	—
2ea	$COCCl_3$	H	**A**	99	<1 : 20	**4e** (99)
2ea	$COCCl_3$	H	**B**	70	1 : 3	—
2fa	CH_2OBn	H	**A**	99	<1 : 20	**4f** (89)
2fa	CH_2OBn	H	**B**	99	1 : 1	—
2ga	H	H	**A**	90	1 : 1	—
2ga	H	H	**B**	99	—[f]	
2gb	H	Me	**A**	60	>20 : 1	—
2gb	H	Me	**A**	65[g]	>20 : 1	**3g** (52)
2gb	H	Me	**B**	99	—[f]	—
2fb	CH_2OBn	Me	**A**	10	n. d.	—
2fb	CH_2OBn	Me	**B**	25	n. d.	—

[a] All reactions conducted in CH_2Cl_2 at 20 °C unless otherwise stated. Conversion and product ratio determined by ^{1}H-NMR spectroscopy of the crude reaction mixture. [b] Reaction in toluene at 110 °C. [c] Reaction at 0 °C. [d] Reaction at 80 °C. [e] Yields of isolated single isomers. [f] Complex mixture, see text. [g] Reaction at 40 °C.

catalyst **B**.[11,12] However, only incomplete conversion was observed in refluxing toluene, probably due to rapid decomposition of the metathesis catalyst at this temperature. When we used **B** for the RCM of allyl ether **2aa**, we made the intriguing observation that a dramatic erosion of selectivity occurred. Five- and six-membered rings are now formed in a ratio close to 1 : 1. Attempts to improve the ratio in either direction by varying the temperature turned out to be completely ineffective; at 0 °C, apparently no conversion took place, while in refluxing toluene, a comparable ratio of products was observed.

In the following step, the influence of a sterically demanding protecting group was investigated. We chose TBDMS and trityl-derivatives **2ba** and **2ca**, respectively. In both cases, virtually perfect selectivity towards the formation of five-membered ring systems **4b** and **4c** was observed with the first generation catalyst **A**. This observation can be understood by assuming that due to the sterically demanding group in the allylic position, virtually no initiation occurs at double bond "b", which is in accord with the high selectivity observed by Michaelis and Blechert for related CM reactions of mono-trityl protected **1**.[12] If, however, initiation at position "b" is blocked, the only possible way to a six membered ring is initiation at "a" and subsequent RCM of the alkylidene intermediate **8** with double bond "b". This ring closure must proceed *via* a ruthenacyclobutane **9**, which is obviously destabilized by strong steric interactions, while in ruthenacyclobutane **10** (resulting from "ac"-ring closure and leading to dihydrofuran **4c**), unfavourable steric interactions are avoided (Scheme 2). With the more reactive catalyst **B**, the amount of six-membered heterocycles is significantly lower (ratios **3** : **4** = 1 : 2 and 1 : 3, respectively) compared to the analogous experiment with benzyl protected **2aa**.



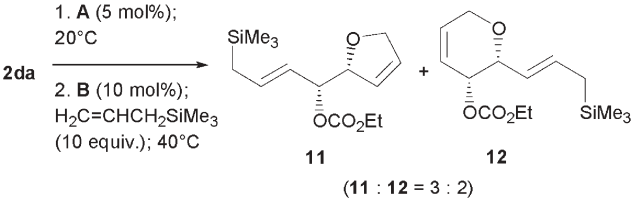
Scheme 2 Rationalization of the preferred selectivity for "ac"-ring closure. L = PCy_3 for precatalyst **A**, L = H_2IMes for precatalyst **B**.

Carbonate **2da** and trichloroacetate **2ea** were then chosen to investigate the effect of electron withdrawing hydroxy protecting groups. While the results obtained for the carbonate **2da** were very similar to those obtained for benzyl ether **2aa**, trichloroacetate **2ea** resembles more closely the TBDMS and trityl-protected derivatives **2ba** and **2ca**. The significantly enhanced selectivity observed for the trichloroacetate group compared to carbonate is not indicative of an electronic effect but is most likely caused by steric differences. Thus, we conclude that electronic effects exerted by the protecting group are negligible, while steric effects play a significant role.

The question remains as to how to explain the remarkably strong influence of the catalyst on ring size selectivity. We assume that intermediate **9** is generally less favorable than intermediate **10**. However, for second generation catalyst **B** (L = H_2IMes in Scheme 2), this difference in energy is apparently less important, presumably due to the overall increased reactivity of second generation catalysts.[18–20]

Alternatively, the high amount of dihydropyrans obtained with catalyst **B** might be the result of a ring opening/ring closing metathesis sequence of the initially formed kinetic product, the dihydrofuran. An experimental hint that such a scenario might play a role in this particular case was observed when dihydrofuran **4d** was subjected to the conditions of a CM reaction. In an attempt to combine the good selectivity for dihydrofuran formation of catalyst **A** with the enhanced reactivity of **B** in CM reactions, **2da** was first treated with first generation catalyst **A** and subsequently, in the presence of allyltrimethylsilane, with second generation catalyst **B**. Under these conditions a 3 : 2 ratio, rather than the expected 10 : 1 ratio, of dihydrofuran **11** to dihydropyran **12** is observed, indicating that ring opening/ring closing steps interfere with the CM reaction (Scheme 3).

From the results discussed so far, it becomes obvious that the only promising approach to selective dihydropyran formation will require exclusive initiation at double bond "b" and subsequent ring closing metathesis with double bond "a". We thought that



Scheme 3 Sequential RCM and CM of **2da** with allyl trimethylsilane.

alkoxymethyl ethers might be able to coordinate the ruthenium and thus act as a catalyst-directing group.[21,22] To evaluate this concept, benzyloxymethyl ether **2fa** was prepared and treated with first and second generation catalysts **A** and **B**. Disappointingly, the results obtained from these experiments do not differ significantly from those discussed above for other protected trienes with respect to conversion and selectivity.

A breakthrough towards the selective formation of a dihydropyran **3** was achieved when the unprotected alcohol **2ga** was treated with first generation catalyst **A**. While, for all the protected derivatives investigated so far, a strong preference (1 : 10 to 1 : 20) for five membered heterocycles **4** had been observed with this particular catalyst, we now found, for the first time, a considerable amount of dihydropyran **3g** (**3g** : **4g** = 1 : 1). This result suggests that the free hydroxy group is obviously capable of directing the metathesis catalyst with considerable selectivity to the closest double bond "b", which finally results in the formation of dihydropyran **3g**. However, the directing effect of the hydroxy group is probably not strong enough to completely overcome the competing initiation at the sterically least hindered double bond "a". Initiation at "a" should, as outlined in Scheme 2, yield both products, with the kinetically preferred formation of dihydrofuran **4**. To eliminate this undesired mode of initiation without changing the structure of the final product, we introduced a methyl group at the terminus of double bond "a". Now, initiation at this disubstituted double bond should be less favorable, and the proposed directing effect of the allylic hydroxy group dominates. This is indeed the case; the RCM of crotyl ether **2gb** with catalyst **A** results in the highly selective formation of dihydropyran **3g**. The dihydrofuran **4g** cannot be detected, even in trace amounts, by means of ^{1}H-NMR spectroscopy of the crude reaction mixture. Conducting the reaction in refluxing dichloromethane does not alter the selectivity but leads to an improved conversion. Treatment of allyl ether **2ga** or crotyl ether **2gb** with second generation catalyst **B** gave a complex mixture of products, which could not unambiguously be analyzed by ^{1}H-NMR-spectroscopy of the crude reaction mixture. Column chromatography and subsequent analysis of the individual fractions revealed that, apart from the monomeric products **3g** and **4g** (obtained as an inseparable 3 : 1 mixture), a self-metathesis product is formed. The composition of the third fraction could not be analyzed, but it seems to contain other CM products of **4g** and **3g**. Once again, this observation shows that the enhanced reactivity of second generation catalyst **B** is associated with a significantly reduced ring size selectivity.

Remarkably, the BOM-protected crotyl ether **2fb** gives, under identical conditions, only poor levels of conversion with both first and second generation catalysts. This observation suggests that the free hydroxy group has not only a directing, but also an activating effect. Given the fact that unprotected allylic alcohols occasionally undergo non-metathesis transformations[23] such as degradation[24] or redox isomerization[25] in the presence of ruthenium carbenes, the enhanced activity of **2gb** compared to its hydroxy-protected analogue **2fb** is somewhat unexpected.

In conclusion, we have shown that the selective metathesis-based syntheses of five- and six-membered oxacycles can be achieved, starting from the same chiral building block. Remarkably, only the less active first generation catalyst **A** gives preparatively useful results, due to the low selectivity observed with second generation catalyst **B**. Key to the high selectivity towards six-membered ring formation is obviously a strong catalyst-directing effect of an unprotected allylic alcohol. It is likely that the results described in this study will have an impact on the interpretation of other selectivity issues in RCM reactions, such as the diastereoselective RCM of divinyl carbinols and other substrates with diastereotopic olefin moieties.[9]

Notes and references

1 R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875.
2 G. C. Fu, S. T. Nguyen, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1993, **115**, 9856–9857.
3 Selected reviews: A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199; S. J. Connon and S. Blechert, *Top. Organomet. Chem.*, 2004, **11**, 93; B. Schmidt and J. Hermanns, *Top. Organomet. Chem.*, 2004, **13**, 223.
4 Review: B. Schmidt and J. Hermanns, *Curr. Org. Chem.*, 2006, **3**, 8, accepted for publication.
5 C. M. Huwe, J. Velder and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2376.
6 B. Schmidt, B. Costisella, R. Roggenbuck, M. Westhus, H. Wildemann and P. Eilbracht, *J. Org. Chem.*, 2001, **66**, 7658.
7 D. J. Wallace, P. G. Bulger, D. J. Kennedy, M. S. Ashwood, I. F. Cottrell and U.-H. Dolling, *Synlett*, 2001, 357; A. S. Edwards, R. A. J. Wybrow, C. Johnstone, H. Adams and J. P. A. Harrity, *Chem. Commun.*, 2002, 1542; C. Baylon, M.-P. Heck and C. Mioskowski, *J. Org. Chem.*, 1999, **64**, 3354.
8 A. H. Hoveyda and R. R. Schrock, *Chem.–Eur. J.*, 2001, **7**, 945; T. J. Seiders, D. W. Ward and R. H. Grubbs, *Org. Lett.*, 2001, **3**, 3225.
9 M. Lautens and G. Hughes, *Angew. Chem., Int. Ed.*, 1999, **38**, 129; B. Schmidt and H. Wildemann, *J. Org. Chem.*, 2000, **65**, 5817; D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U.-H. Dolling and P. J. Reider, *Org. Lett.*, 2001, **3**, 671.
10 Review on group-selective reactions: R. W. Hoffmann, *Synthesis*, 2004, 2075.
11 K. J. Quinn, A. K. Isaacs and R. A. Arvary, *Org. Lett.*, 2004, **6**, 4143; K. J. Quinn, A. K. Isaacs, B. A. DeChristopher, S. C. Szklarz and R. A. Arvary, *Org. Lett.*, 2005, **7**, 1243.
12 S. Michaelis and S. Blechert, *Org. Lett.*, 2005, **7**, 5513.
13 M.-A. Virolleaud and O. Piva, *Synlett*, 2004, 2087.
14 Review: A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307.
15 T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang and H. Zhao, *J. Am. Chem. Soc.*, 2004, **126**, 10210.
16 J. C. Sierra, D. Hüerländer, M. Hill, G. Kehr, G. Erker and R. Fröhlich, *Chem.–Eur. J.*, 2003, **9**, 3618.
17 D. J. Wallace, *Tetrahedron Lett.*, 2005, **46**, 591–594; V. Böhrsch, J. Neidhöfer and S. Blechert, *Angew. Chem., Int. Ed.*, 2006, **45**, 1302.
18 M. S. Sanford, J. A. Love and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 6543.
19 C. Adlhart and P. Chen, *Angew. Chem., Int. Ed.*, 2002, **41**, 4484.
20 B. F. Straub, *Angew. Chem., Int. Ed.*, 2005, **44**, 5973.
21 For the application of a catalyst-directing group in selective hydroformylation, see: B. Breit, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2835.
22 Michaelis and Blechert investigated a directing effect of a methoxymethyl group in the RCM of acrylate **5** (R = H, PG = MOM) and observed a low ratio of six- to five-membered ring lactone of 1 : 2.7,[12] while Quinn *et al.* could not detect any six-membered ring lactone when using non-coordinating protecting groups such as TBDMS or benzyl[11].
23 B. Schmidt, *Eur. J. Org. Chem.*, 2004, 1865.
24 T. R. Hoye and H. Zhao, *Org. Lett.*, 1999, **1**, 1123.
25 M. K. Gurjar and P. Yakambram, *Tetrahedron Lett.*, 2001, **42**, 3633.