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Unusual Influence of Substituents on Ring-Opening Metathesis Reactions

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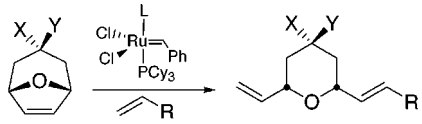
ABSTRACT

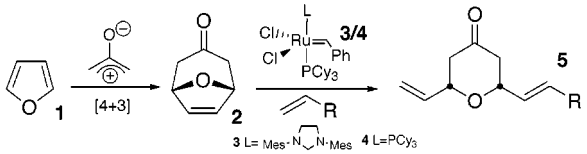


The ring-opening cross-metathesis of oxabicyclo[3.2.1]octene derivatives provides a convenient method for preparing differentially substituted 4-pyrones. The major competing reaction is the ring-opening metathesis polymerization of the bridged olefin. Studies on this reaction have shown that substituents on the bicyclic alkene can have a dramatic influence on the competing reactions.

The ring-opening metathesis (ROM) reaction has become a powerful method used to convert cyclic olefins to acyclic dienes.[1] However, the subsequent cross-metathesis reaction is in competition with the formation of polymers through the ring-opening metathesis polymerization (ROMP) process. Frequently, the oligomerization of the cyclic alkene can be suppressed by the addition of a large excess of a donor olefin, with more nucleophilic alkenes providing superior results.[2] During an investigation on the ring-opening metathesis of 8-oxabicyclo[3.2.1]octene derivatives, we have observed that the efficiency of the process can be influenced by functionality on the oxabicyclic olefin.

The oxabicyclo derivative **2**, conveniently prepared by [4+3]-cycloaddition with furan[3] (**1**), is a powerful building block that can lead to functionalized furan, pyran, and cycloheptane derivatives through scission of one of the three unique bridges. We have been interested in developing an efficient strategy to prepare unsymmetrical 2,6-disubstituted pyrans **5** by opening the unsaturated bridge[4] through an olefin metathesis reaction (Scheme 1).

Scheme 1. Synthesis of Disubstituted Pyrans by ROM



The tetrahydropyran moiety is found in a variety of natural products such as forskolin[5] and latrunculin[6] and is an important target for new synthetic strategies. The ROM strategy could be used either in an intermolecular process to prepare cis-disubstituted pyrans or in an intramolecular fashion to prepare fused pyran rings. Herein, we report our investigation of the intermolecular process.[7]

Initial studies were conducted on the parent ketone **2**.[8] Control experiments indicated that **2** could be polymerized

(1) For reviews on olefin metathesis, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. Wright, D. L. *Current Org. Chem.* **1999**, *3*, 211. Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

(2) For examples, see: Tallarico, J.; Randall, M. L.; Snapper, M. L. *Tetrahedron* **1997**, *53*, 16511. Tallarico, J.; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1997** *119*, 7157.

(3) For excellent reviews, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. Noyori, R.; Hayakawa, Y. *Tetrahedron* **1985**, *41*, 5879; Mann, J. *Tetrahedron* **1986**, *42*, 4611. Rigby, J. H.; Pigge, F. C. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley and Sons: New York, 1997; Vol. 51, p 351. Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217.

(4) For some alternative openings, see: Dunkel, R.; Mentzel, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 14929. Wolkers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *53*, 1905.

(5) Bhat, S. V.; Bajwa, B. S.; Dornauer, H.; Fehlhaber, H. W. *Tetrahedron Lett.* **1977**, *18*, 1669.

(6) Kashman, Y.; Groweiss, A.; Shueli, J. *Tetrahedron Lett.* **1980**, *21*, 3629.

(7) Two examples have been reported, with *p*-tBu styrene (Cuny, G. D.; Cao, J.; Sidhu, A.; Hauske, J. R. *Tetrahedron* **1999**, *55*, 8169) and with ethylene (Harmata, M.; Shao, L.; Kurti, L.; Akeywardane, A. *Tetrahedron Lett.* **1999**, *40*, 1075).

(8) Fohlisch, B.; Gehrlach, E.; Geywitz, B. *Chem. Ber.* **1987**, *120*, 1815.

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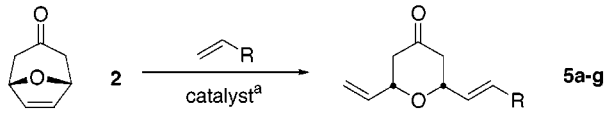
in solution, but the reaction was slow. Donor alkenes were selected with a range of functionality to probe the influence of the substituent on the efficiency of the cross-metathesis reaction. Optimal conditions were found to be the addition of 5 equiv of the alkene and 1 mol % of the Grubbs' catalyst **3**[9] to a solution of **2** in chloroform (Table 1).

Table 1. Ring-Opening Metathesis of Bicyclic Ketone **2**



pyran	alkene	R	catalyst[b]	*E*/*Z*	yield[c]
5a	styrene	Ph−	3	>95	83%
5b	2-bromostyrene	*o*-BrPh−	3	>95	65%
5c	1-hexene	$CH_3(CH_2)_3$−	4	>95	89%
5d	allyl bromide	$BrCH_2$−	3	>95	71%
5e	4-bromo-1-butene	$BrCH_2CH_2$−	3	>95	72%
5f	methacrylate	MeO_2C−	3	>95	33%
5g	acrylonitrile	NC−	3	>95	10%

[a] Reaction conditions: 5 equiv of alkene, 1 mol % catalyst, 0.3 M in $CDCl_3$. [b] See ref 9. [c] Isolated yields of pure *E*-alkenes.

The cross-metathesis reactions were highly selective for the formation of the *E*-alkenes[10] with any *Z*-isomer being removed by chromatography. The efficiency of the cross-metathesis depended heavily upon the nature of the donor alkene used in the reaction. Electron-rich olefins such as styrene or 1-hexene were very effective partners in the metathesis. However, electron-deficient alkenes resulted in a significant attenuation in yield. Cross-metathesis with methacrylate gave only 33% of **5f**, despite a large excess of the donor. Acrylonitrile, reported to be a poor substrate in these reactions,[11] produced only small amounts of the corresponding nitrile.

Interestingly, in each example the reaction failed to reach completion, despite prolonged reaction times, elevated temperatures, or increased catalyst loading. Since styrene was an effective donor and has distinctive NMR signals, this ROM reaction was examined in greater detail. These reactions are conveniently monitored by NMR spectroscopy, and it was demonstrated that the reaction was in fact an equilibrium process. For example, once equilibrium was reached (approximately 90% completion by NMR), the addition of more starting materials resulted in a rapid return to the equilibrium ratios. In order for this reaction to be in equilibrium, it must be reversible. This was demonstrated by exposing diene **5a** to catalyst **3**. Within several minutes of catalyst addition, the bicyclic ether **2** and styrene were observed by NMR.

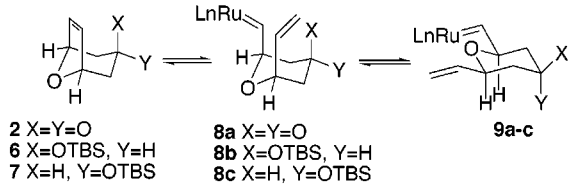
(9) Catalyst **3** was superior to **4** in all cases except 1-hexene, where lower yields resulted from a second cross-metathesis between **5c** and 1-hexene. For catalyst **3**, see: Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(10) Olefin assigned by coupling constant or NOE analysis.

(11) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

In an attempt to force the reaction to completion, it was postulated that pyran ring substituents could help render the process irreversible (Scheme 2). One possible scenario is that

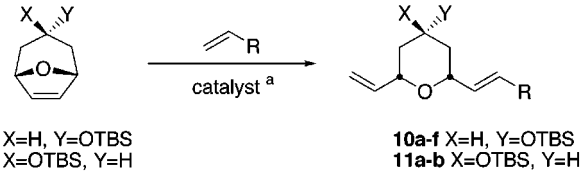
Scheme 2. Reversibility of the ROM Reaction



initial opening occurs to give **8a**−**c**, and then the pyran undergoes ring inversion to give conformers **9a**−**c** where both bulky groups can occupy equatorial positions. In order for the reverse reaction (ring-closing metathesis) to proceed, the two unsaturated appendages must adopt a diaxial relationship as in **8a**−**c**.

Conformation **8a** is destabilized by only one set of diaxial interactions. However, if the ketone is converted to an sp^3 center as in **8b**, an additional set of destabilizing diaxial interactions is introduced. This should render conformation **9b** more favorable and prevent ring closure. A model substrate was prepared by selective reduction of the C3-ketone to the endo alcohol and conversion to the bulky silyl ether **6**.[12] In accordance with this rationale, ring opening of **6** with styrene reached completion within 10 min and no residual starting alkene could be observed by NMR. Furthermore, exposure of the ring-opened product **10a** to Grubbs' catalyst **3** provided no ring closure, even after 24 h. The ring-opening cross-metathesis of the reduced derivatives **6** and **7** was studied with various donor alkenes (Table 2).

Table 2. Ring-Opening of Reduced Derivatives



pyran	alkene	R	catalyst[b]	*E*/*Z*	yield[c]
10a	styrene	Ph−	3	>95	60%
10b	2-bromostyrene	*o*-BrPh−	3	>95	18%
10c	1-hexene	$CH_3(CH_2)_3$−	4	>95	63%
10d	allyl bromide	$BrCH_2$−	3	>95	62%
10e	4-bromo-1-butene	$BrCH_2CH_2$−	3	>95	56%
10f	methacrylate	MeO_2C−	3		0%
11a	styrene	Ph−	3	>95	67%
11b	1-hexene	$CH_3(CH_2)_3$−	4	>95	75%

[a] Reaction conditions: 5 equiv of alkene, 1 mol % catalyst, 0.3 M in $CDCl_3$. [b] See ref 9. [c] Isolated yields of pure *E*-alkenes.

Surprisingly, the cross-metathesis products were generated in lower yield when compared with the ketone **2**. Addition-

ally, it was observed that the small differences between the quality of the donor alkenes became greatly exacerbated in the ring opening of **6**. For example, a slight decrease in yield is observed between styrene and α-bromostyrene in the ring opening of **2** (Table 1). However, this difference becomes much greater in the ring opening of **6** where styrene gave a 60% yield, while 2-bromostyrene dropped off to a mere 18% yield. Moreover, while methacrylate produced modest yields with **2**, no product could be observed in the reaction with **6**. It appeared that in these cases, oligomerization of the starting material had now become a competitive reaction and, with poorer donors, the yield of the desired product decreased sharply.[13] In addition to affecting the position of equilibrium, the presence of an sp^3 center had apparently rendered the alkene much more reactive toward ring-opening polymerization. To establish the enhanced reactivity, a competition experiment was conducted on the two model alkenes. Treatment of a mixture of **2** and **6** with catalyst **3** showed that the reduced derivative **6** was completely converted to oligomeric material while ketone **5** remained largely unreacted (Figure 1).

Further studies with *exo*-silyl ether **7**[14] showed that even if the large group occupied the equatorial position, as in **8c**, the enhanced reactivity was still observed. There was no evident reversibility with **11a**, consistent with **9c** as the favored conformation. Competition experiments between **2** and **7** were identical to those between **2** and **6**. The simple change in hybridization at C3 appears to be responsible for the change in reactivity and is independent of the position of the large silyl ether. Although the yields with styrene and 1-hexene were slightly better when **7** was used (Table 2), the ketone **2** is the substrate of choice for the synthesis of pyrans.

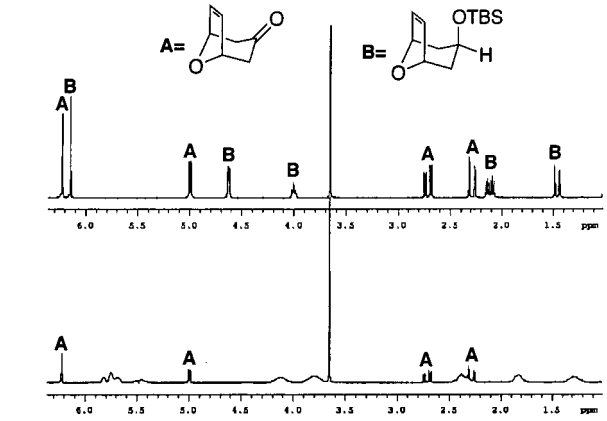


Figure 1. Upper spectrum is an equal mixture of **2** and **6**. The lower spectrum was recorded 20 min after addition of 1 mol % catalyst **3**. The peaks corresponding to **6** are absent from the lower spectrum, and the formation of polymer is observed. The peak at 3.67 ppm is 1,4-dioxane added as an internal standard.

These unusual effects have a significant impact on the synthetic efficiency of the ring-opening cross-metathesis reaction. Alternatively, the increased reactivity of the reduced derivatives could prove to be beneficial in the synthesis of ROMP polymers. Further studies on these effects and the intramolecular variation of this process are ongoing.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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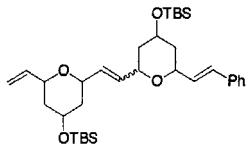
(12) Compund **6** was prepared from **2** by the following sequence: (i) L-selectride, −78 °C, THF; (ii) TBSOTf, lutidine.

(13) The dimer shown was characterized as a major byproduct in the ring opening of **6** with styrene. The presence of higher oligomers was also observed.



(14) Prepared from **2** by the following sequence: (i) L-selectride −78 °C; (ii) PPh_3, DEAD, $PhCO_2H$; (iii) KOH, MeOH; (iv) TBSOTf, lutidine.