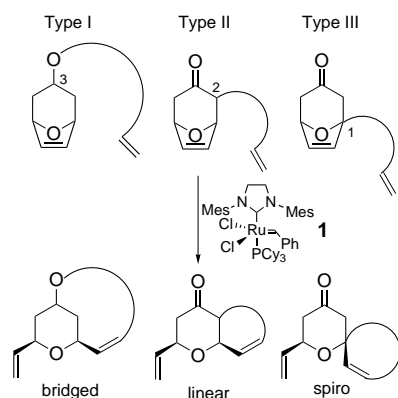


Synthesis of Functionalized Pyrans by Domino Metathesis Reaction of Oxabicyclo Derivatives: Dramatic Effect of Remote Substituents on Reactivity and Selectivity**

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Highly substituted pyrans are a common structural feature found in natural products and have been the focus of many synthesis studies.^[1] They are often present as an integral part of macrocyclic structures of marine origin. We previously reported^[2] a general method for the preparation of *cis*-2,6-disubstituted-4-pyrones through the intermolecular ring-opening cross-metathesis reaction of 8-oxabicyclo[3.2.1]octene derivatives, which are conveniently prepared by the [4+3] cycloaddition between furan and an oxyallyl cation equivalent.^[3] A more advanced variation occurs when the donor olefin is tethered to the bicyclic ring system. The second metathesis process would effect a ring closure, thereby resulting in the synthesis of annulated pyran systems. In principle, there are three manifolds for this bond-reorganization process, determined by placement of the tether (Scheme 1).^[4]

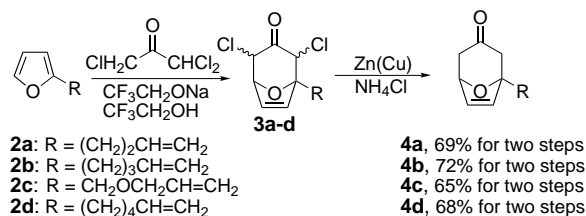


Scheme 1. Synthesis of fused pyrans by metathesis-promoted bond reorganization.

A type I bond-reorganization process would arise if the tether was attached at C3, leading to the synthesis of bridged fused pyrans. Placement of the tether at C2 leads to a linear fused system, whereas a type III cyclization from the C1 position would lead to spiro-fused pyrans. Herein, we wish to report our studies on the type III cyclization and the dramatic influence of remote substituents on the domino process. These compounds are of interest as building blocks for natural

product syntheses^[5] and as novel scaffolds for combinatorial libraries.^[6]

To examine the facility of this process, a series of oxabicyclo[3.2.1]octan-3-one derivatives with an olefinic tether at the bridgehead were prepared by oxyallyl cation cycloaddition of 2-substituted furans (Scheme 2). Reaction



Scheme 2. Synthesis of substituted bicyclic ethers.

of the furans under the conditions of Föhlisch et al.^[7] led to a smooth conversion into the oxabicyclo[3.2.1]octenes **3a–d**. Direct dechlorination upon exposure to zinc–copper couple gave the metathesis precursors **4a–d** in good yields. With a series of dienes in hand, we were able to study the domino metathesis process (Table 1).

Table 1. Synthesis of spirocyclic pyrans.

Alkene	Product ^[a]	Yield [%] ^[b]
4a	5a	56 (16)
4b	5b	82 (10)
4c	5c	80
4d	5d	< 15 (44) ^[c]

[a] Reaction conditions: substrate in CH_2Cl_2 (0.01M), **1** (2 mol %). [b] Yield of recovered starting material in parentheses. [c] The dimer was also isolated (38 %).

Exposure of a dilute solution of the dienes **4a–c** to the Grubbs catalyst **1**^[8] led to rearrangement to the corresponding five- and six-membered spirocycles **5a–c** in good yield. Cyclization to form the seven-membered homologue **5d** was extremely poor, the major product arising from dimerization of the terminal vinyl groups. Furthermore, much of the starting alkene was recovered unchanged. Increased catalyst or elevated temperatures did little to improve the yield of the reaction.

This method is also compatible with the analogous oxabicyclo[2.2.1]heptene derivatives leading to perhydro-spirofur-

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[**] We thank the National Science Foundation for support of this work. MEJ thanks the University of Florida for a graduate minority fellowship. We thank Professor Merle A. Battiste and Professor William R. Dolbier for helpful discussions.

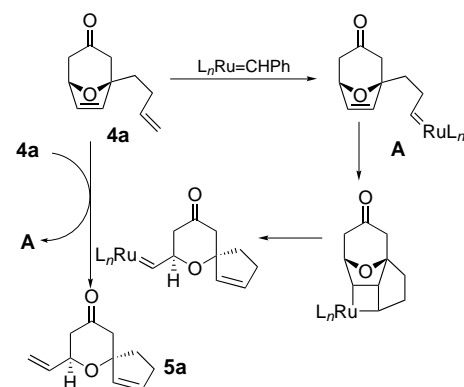
ans. The substrates were easily prepared from furans **2a–d** by Diels–Alder reaction with *N*-phenylmaleimide. The major *exo* adducts were treated with the Grubbs catalyst to trigger rearrangement (Table 2). The reactions of these derivatives delivered the rearranged furans **7a–d** in moderate to excellent yields. Again, five- and six-membered cyclizations were the most efficient. Interestingly, the formation of the seven-membered ring **7d** was significantly better in this series. This could be related to the enhanced reactivity of the more strained oxabicyclo[2.2.1]heptene nucleus.

Table 2. Synthesis of spirocyclic perhydrofurans.

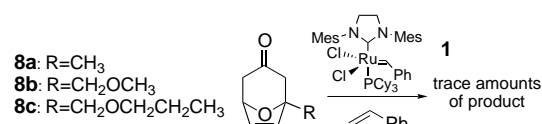
Alkene	Product ^[a]	Yield [%] ^[b]
6a	7a	84
6b	7b	78
6c	7c	95
6d	7d	54 (19)

[a] Conditions: substrate in CH_2Cl_2 (0.01M), **1** (2 mol %). [b] Yield of recovered starting material in parentheses.

One possible mechanism^[9] involves initial reaction with the vinyl group followed by cyclization to close the carbocyclic ring and open the bicyclic olefin simultaneously (Scheme 3). An alternative path would require a regioselective opening of the bridged olefin followed by cyclization onto the pendant olefin. Since the reactions had proceeded cleanly and in high yield, we favored the former mechanism. However, there is little information regarding the influence of bridgehead substituents,^[10] and we felt that the intermolecular variant



Scheme 3. Proposed mechanism for the domino metathesis reaction.



Scheme 4. Attempted ring-opening of substituted systems.

offered an opportunity to probe these regiochemical issues (Scheme 4).

Surprisingly, exposure of the substituted compounds **8a–c** to catalyst and styrene gave only trace amounts of product, even after prolonged reaction times and elevated temperatures. In fact, the compounds could not even be forced to undergo ROMP in refluxing toluene. The inability to effect ring-opening of these systems may be related to shielding of the *exo* face of the olefin by the bridgehead group. This suggests that the intramolecular reaction proceeded by initial reaction with the terminal olefin. Since ensuing attack at the bridge alkene would be intramolecular, it would be less sensitive to these steric effects.

In previous studies,^[2] an unusual influence of the group at C3 was observed: reduction/silylation of the ketone greatly increased the reactivity of the bicyclic alkene towards ring opening. It seemed possible that this remote effect may be used to induce reactivity in the unreactive olefins. To examine this possibility, a series of reduced derivatives was prepared^[11] and subjected to metathesis conditions (Table 3).

Table 3. Intermolecular cross-metathesis of reduced derivatives.

Alkene ^[a]	R	X	Y	Yield [%]	10/11 ^[b]
9a	Me	OTBS	H	83	6:1
9b	CH_2OMe	OTBS	H	65	1:1
9c	Me	OH	H	85	20:1
9d	CH_2OMe	OH	H	66	20:1
9e	Me	H	OH	15	6:1

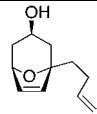
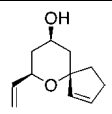
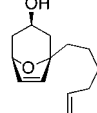
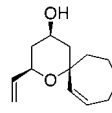
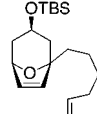
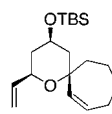
[a] Conditions: substrate in CH_2Cl_2 (0.3M), styrene (3–4 equiv), **1** (1.5 mol %). [b] Ratios approximated by NMR spectroscopy and GC analysis.

Reduction/silylation of ketones **8a** and **8b** gave adducts **9a/9b**. As previously observed, this structural change resulted in a dramatic change in reactivity. Both compounds opened readily with styrene to give the cross-metathesis products **10/11**. The methyl-substituted compound **9a** showed good regioselectivity, giving the more substituted isomer **10a** as the major product (6:1). The methoxymethyl derivative **9b** was not selective, thus giving an almost equal mixture of the two regioisomers. In a very surprising result, opening of the *endo* alcohols **9c/9d** with styrene, although a much slower reaction, showed a dramatic increase in regioselectivity, producing the more substituted derivatives **10c/10d** in an approximately 20:1 predominance. This high selectivity was lost when the reactions were run at higher temperatures or in

the presence of a larger excess of catalyst. The origin of this enhanced reactivity and selectivity appears to be an exclusive *endo* effect. Opening of the *exo* alcohol **9e** was extremely sluggish, only proceeding to about 15%. Moreover, the regioselectivity of the product had decreased to a ratio of about 6:1. These effects could be a result of the steric interaction of the axial group with the bridged alkene or an electronic effect similar to those seen in norbornyl systems.^[12]

Although the nature of the effect is unclear, we proposed that this rate acceleration could be used to improve some of the previous spirocyclizations. If the reaction proceeds as in Scheme 3, then the second ring-closing step should be accelerated by similar structural changes. Therefore, we examined the spirocyclization with reduced forms of dienes **4a** and **4d** (Table 4). We examined the five- and seven-membered ring closures, since these were less efficient than

Table 4. Spirocyclizations with reduced derivatives.

Alkene	Product ^[a]	Yield ^[b]
12 	13 	83 %
14 	15 	48 %
15 	17 	80 %

cyclizations to form cyclohexyl rings. In the case of cyclopentyl rings it may be somewhat difficult for the shorter tether to reach the bridged alkene, whereas the seven-membered ring may be slowed by nonbonded interactions in the tether. Diene **4a** was reduced to the *endo* alcohol **12**, and rearrangement gave **13** in an improved yield of 83%. The more difficult cyclization to form the seven-membered ring systems was also better with *endo* alcohol **14**, tripling the yield to 48%. Since the silyl ethers were more reactive in the intermolecular case, it seemed possible that an even better rate enhancement could be produced. Treatment of **16** with the ruthenium catalyst resulted in a rapid reaction, delivering the spiro product **17** in 80% yield. This study nicely illustrates the potential of tuning alkene reactivity in these types of reactions.

Olefin-metathesis reactions have become important bond-forming reactions in contemporary synthetic chemistry. Domino ring-opening/ring-closing reactions are a convenient way to construct polycyclic systems from readily available bridged bicyclic alkenes. We have been able to develop a method to prepare spiro-annulated pyrans from furan. An important aspect of this study is the finding that the reactivity and selectivity of the metathesis reactions can be tuned by manipulation of functional groups on the substrate. Although the origins of these effects are still under investigation, it is clear that they can play an extremely important part in

metathesis reactions. Further studies on these effects and the synthesis of other types of annulated pyrans are currently under investigation.

Received: July 8, 2002 [Z19679]

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