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Highly Regioselective Ring-Opening/Cross-Metathesis Reactions of 2-Sulfonylnorbornene Derivatives

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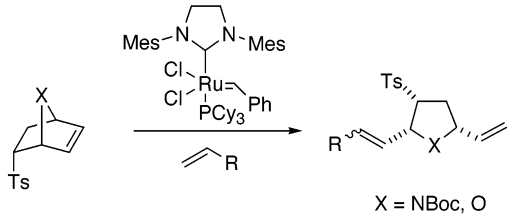
ABSTRACT



Tandem ring-opening/cross-metathesis (ROM/CM) reactions of norbornenes can be a powerful entry into highly substituted organic molecules. However, their utility has been limited largely to symmetrical norbornenes because of the general lack of regioselective variants of these reactions. This manuscript describes our successful attempts to address this issue through the use of a sulfone to direct the ROM/CM reaction of a 7-azanorbornene and a 7-oxanorbornene.

Developments in transition metal-catalyzed olefin metathesis have had a dramatic impact on the field of chemical synthesis.[1] Among the various metathetical-based processes, the ring-opening/cross-metathesis (ROM/CM) reaction of norbornene analogues has received a significant amount of attention both because of the ease with which these substrates undergo ROM reactions and because the ROM/CM reaction is a powerful entry into highly substituted five-membered rings.[2] Despite this, problems associated with the general lack of regioselectivity when unsymmetrical norbornenes are used must be overcome before the reaction can become of general use to the chemical synthesis community.[3−6]

In considering methods of improving the reaction, we were drawn to the possibility that norbornenes having the appropriate heteroatom substitution might show enhanced levels of regioselectivity either through heteroatom chelation to the ROM/CM catalyst or via more subtle remote substituent effects.[7,8] With this in mind, we became interested in 2-sulfonyl-7-azanorbornenes and were surprised to find no reports of the use of any 7-azanorbornenes in ROM/CM

(1) For recent reviews, see: (a) Grubbs, R. H.; Trnka, T. M.; Sanford, M. S. *Curr. Meth. Inorg. Chem.* **2003**, *3*, 187. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(2) For a recent review on the use of norbornenes in ROM/CM sequences, see: Arjona, O.; Csákÿ, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611.

(3) The state of the art in this area is Arjona and Plumet's use of 2-substituted 7-oxanorbornenes to give ca. 4:1 mixtures of tetrahydrofuran regioisomers. See: Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 9739.

(4) Other than with the cyclopentadiene dimer, regioselective ROM/CM reactions of 2-substituted norbornenes have not been identified; see: (a) Mayo, P.; Tam, W. *Tetrahedron* **2002**, *58*, 9513. (b)

(5) For ROM/CM reactions of 2-azanorbornenes, see: (a) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257. (b) Ishikura, M.; Saijo, M.; Hino, A. *Heterocycles* **2002**, *57*, 241.

(6) An alternative is to desymmetrize symmetrical norbornenes. For a recent review that includes a discussion of this topic, see: (a) Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.

(7) Chelation of heteroatoms to Ru has been proposed to be important in other metathetical processes. See refs 1−3 and: (a) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (b) Paquette, L. A.; Fabris, F.; Tae, J.; Gallucci, J. C.; Hofferberth, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 3391. (c) Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545.

(8) Remote substituent effects on regioselective reactions are well documented with norbornene derivatives; see for example: (a) Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341. (b) Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 7338. (c) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031.

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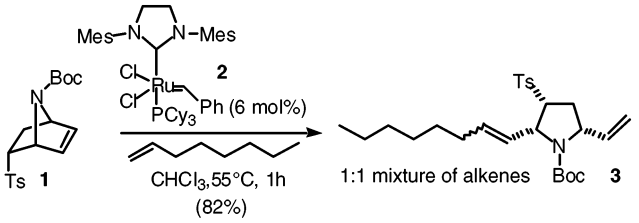
processes.[5] Thus, not only would this work enable us to examine the possible influence of a sulfonyl group on the reaction but, if successful, it would also serve to broaden the scope of substrates capable of undergoing ROM/CM and potentially lead to the efficient synthesis of a variety of highly substituted pyrrolidine-containing alkaloids.[9]

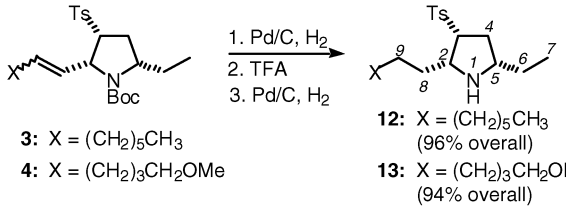
As a test substrate to examine the issues outlined above, 2-tosyl-7-azanorbornene **1** was generated in two steps from the Diels−Alder cycloaddition of *N*-Boc pyrrole and tosylacetylene followed by selective reduction according to Muchowski's protocol.[10] Gratifyingly, when **1** was exposed to ROM/CM conditions with 1-octene (5 equiv) and **2** (6 mol %),[11] pyrrolidine **3** was isolated in 82% yield (eq 1). On the basis of previous reports with the corresponding norbornene and 7-oxanorbornene analogues, it was not surprising to us that **3** was isolated as a 1:1 mixture of (*Z*)- and (*E*)-alkene isomers.[1−5] However, as all previous examples had delivered only moderate levels of regioselectivity, we were somewhat surprised to find that both the (*Z*)- and (*E*)-alkene products had come from the same ROM regioisomer. Ultimately, we were pleased both by this and by the observation that the reaction had generated the regioisomer having the tosyl group proximal to the internal olefin. The sense of selectivity seen here is novel; to the best of our knowledge, the major regioisomer from all other ROM/CM reactions of norbornene derivatives have the terminal alkene proximal to the large substituent.[1−4]



(eq 1)

The ROM/CM reaction of **1** turned out to be quite general. The reaction of **1** with 5-hexenylmethyl ether or 4-bromobutene in the presence of **2** gave pyrrolidines **4** and **5** in 92 and 84% yields, respectively (entries 2 and 3). The use of methyl pent-4-enoate gave a 49% yield of pyrrolidine **6** (entry 4). The yield of **6** was increased to 71% when the amounts of **2** (10 mol % in three portions) and olefin (15 equiv in three portions) were increased (entry 5). Using unoptimized conditions, methyl hex-5-enoate, hex-5-en-2-one, allylsilane, and the TBS ether of 5-hexen-1-ol gave pyrrolidines **7**−**10** in 56, 58, 56, and 45% yields (entries 6−9), respectively, when subjected to **1** and **2**. As vinyl acetates are notoriously poor substrates for cross-metathesis reactions,[15] we were pleasantly surprised to find that **2** also catalyzed the ROM/CM between **1** and vinyl acetate to give **11** in 66% yield (eq 2).[16]

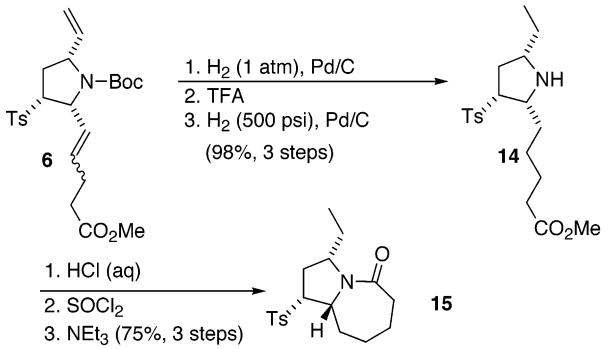
For pyrrolidines **3** and **4**, we were able to elucidate the structure of the products from the ROM/CM reactions only after reduction of the alkenes and removal of the Boc group (eq 2). Subsequently, the regiochemistry of **12** and **13** was established spectroscopically.[16,17]



(eq 2)

The regio- and stereochemistry of pyrrolidine **6** was also established spectroscopically after its conversion into pyrrolidine **14** and subsequently fused pyrrolo[1,2-*a*]azepine **15** (Scheme 1). As an aside, the presence of the pyrroloazepine

Scheme 1



ring system in interesting alkaloids (i.e., lehmizidines, stemona alkaloids) speaks to one possible utility of these reactions.[18,19]

To get a better sense of the influence of the sulfone on the reaction, we next examined 7-azanorbornene analogue

(9) For reviews covering the generation of nitrogen-containing compounds using RCM, see: (a) Walters, M. A. Recent Advances in the Synthesis of Heterocycles via RCM. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Elmsford, NY, 2003; Vol. 15, p 1. (b) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.

(10) Leung,-Toung, R.; Liu, Y.; Muchowski, J. M.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 3235.

(11) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(12) Other examples of regioselective ROM/CM reactions include Snapper's cyclobutene ROM/CM reactions; see: (a) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478. (b) Tallarico, J. A.; Bonitatebus, P. J., Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157.

(13) See refs 1−3 and: Arjona, O.; Csákÿ, A. G.; Plumet, J. *Synthesis* **2000**, 857.

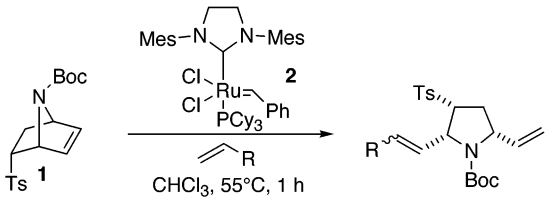
(14) In the case of substrates also having bridgehead substitution, Arjona and Plumet observed high levels of regioselectivity but at the expense of low overall conversions. See ref 2.

(15) Grubbs has reported that vinyl acetates do not undergo cross-metathesis with **2**; see: Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.

(16) For **11**−**14** and **20**, COSY cross-peaks were observed between H(7) and H(6), H(6) and H(5), H(5) and H(4), H(4) and H(3), and H(3) and H(2). For compound **13**, NOE enhancements were observed between H(2) and H(5) and between H(5) and H(3).

(17) Regiochemistries of pyrrolidines **5** and **7**−**10** were assigned on the basis of the similarity of their spectra to those of **3**, **4**, **6**, and **11**.

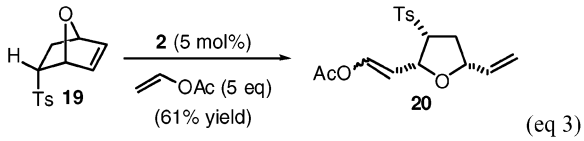
Table 1. ROM/CM of *endo*-Sulfone **1**



entry	R	2	pyrrolidine[a]	yield
1	$(CH_2)_5CH_3$ (5 equiv)	6 mol %	**3**	82%
2	$(CH_2)_3CH_2OMe$ (5 equiv)	10 mol %	**4**	92%
3	CH_2CH_2Br (5 equiv)	6 mol %	**5**	84%
4	$(CH_2)_2CO_2Me$ (5 equiv)	6 mol %	**6**	49%
5	$(CH_2)_2CO_2Me$ (15 equiv)	10 mol %	**6**	71%
6	$(CH_2)_3CO_2Me$ (5 equiv)	6 mol %	**7**	56%
7	$(CH_2)_2C(O)Me$ (5 equiv)	10 mol %	**8**	58%
8	$(CH_2)TMS$ (10 equiv)	10 mol %	**9**	56%
9	$(CH_2)_2CH_2OTBDMS$ (10 equiv)	10 mol %	**10**	45%
10	OAc (5 equiv)	15 mol %	**11**	66%

16 having an exocyclic sulfone at C(2) (Table 2).[20] The Ru-catalyzed coupling of **16** with both 1-octene and methyl pent-4-enoate resulted in a 1:1 mixture of regioisomers **17** and **18** in 70 and 30% yields, respectively.[21] These experiments clearly demonstrate the importance of the position of the sulfone on the regioselectivity.

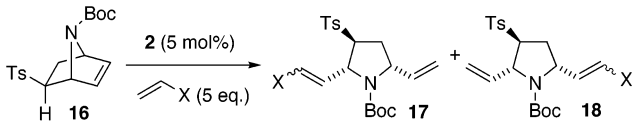
Additional evidence for the importance of the sulfone came from the reaction of 2-sulfonyl-7-oxanorbornene **19**. In contrast to Arjona and Plumet's experiments with 2-acetoxy-7-oxanorbornenes and other similarly substituted substrates,[3] the reaction of **19** with vinyl acetate resulted in the formation of furan **20** as a single regioisomer in 61% yield. As was the case with **1**, the sense of regioselectivity observed with **19** is the opposite of that seen by Arjona and Plumet.



(eq 3)

In conclusion, we have found that 2-tosyl-7-azanorbornene and 2-tosyl-7-oxanorbornene ROM/CM reactions result in the stereoselective generation of 2,3,5-trisubstituted pyrrolidines and furans, respectively. Our current efforts are directed at gaining a better understanding of the directing ability of sulfones in these processes as well as utilizing the products from these reactions in complex molecule synthesis.

Table 2. ROM/CM of *exo*-Sulfone **16**



X	yield	**17**:**18**
$(CH_2)_5CH_3$	70%	1:1
$(CH_2)_2CO_2Me$	30%	1:1

Acknowledgment. We are grateful to the NSF (CAREER AWARD to J.D.R.) and the University of Utah for support of this research. The authors would like to thank Professor Janis Louie (University of Utah) and Dr. Chris Bielawski (California Institute of Technology) for helpful conversations. The authors would also like to thank Dr. Charles Mayne for help with NMR experiments.

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

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(18) Lehmizidine alkaloids: Garraffo, H. M.; Jain, P.; Spande, T. F.; Daly, J. W.; Jones, T. H.; Smith, L. J.; Zottig, V. E. *J. Nat. Prod.* **2001**, *64*, 421.

(19) Stemona alkaloids: Pilli, R. A.; da Conceição Ferreira de Oliveira, M. *Nat. Prod. Rep.* **2000**, *17*, 117.

(20) Azanorbornene **16** was a minor product formed during the generation of **1**.

(21) Determined following removal of the Boc group and global hydrogenation.