

# Regioselective Ring-Opening/ Cross-Metathesis Reactions of Norbornene Derivatives with Electron-Rich Olefins

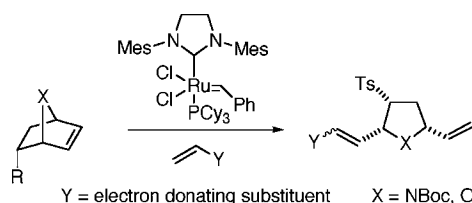
Zhuqing Liu and Jon D. Rainier\*

Department of Chemistry, University of Utah, 315 S 1400 E,  
Salt Lake City, Utah 84112

rainier@chem.utah.edu

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## ABSTRACT



This manuscript describes facile ring-opening/cross-metathesis (ROCM) reactions between unsymmetrical norbornene derivatives and electron-rich olefins in the presence of the second-generation Grubbs' catalyst to generate highly substituted furans and pyrroles.

Because they result in the rapid generation of complex skeletons from relatively simple starting materials, metal alkylidene-catalyzed ring-opening/cross-metathesis (ROCM) reactions of norbornenes have drawn the attention of the synthetic community.<sup>1</sup> Despite this attention, problems remain, including one that has attracted us: the use of electron-rich olefins.<sup>2</sup> In fact, with the exception of the use of vinyl sulfides and vinyl selenides by Katayama, Ozawa, and co-workers and our recent work with vinyl acetate,<sup>3,8</sup> attempts to employ electron-rich olefins in CM or ROCM have generally failed.<sup>4</sup> Presumably, this is due to the facile

conversion of the Schrock carbene catalysts that are generally used in these transformations into relatively unreactive Fischer carbenes.<sup>5</sup> In support of this notion, the use of vinyl ethers in metathesis-based processes (other than ring-closing metathesis) has been limited to the capping of ring-opening metathesis polymerizations (ROMP).<sup>6</sup>

In the course of investigating the chemistry of 7-aza- and 7-oxanorbornenes, we recently reported that they underwent ROCM reactions with vinyl acetate in the presence of 6 mol % Grubbs' second-generation Ru alkylidene (Grubbs 2) **3**.<sup>7,8</sup> We were intrigued by the possible synthetic and mechanistic implications of this result and decided to examine its scope. In particular, we became interested in asking whether other electron-rich olefins might also participate in this transformation. The results of our efforts to answer this question are described here.

(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.; Csáky, A. G.; Plumet, J. *Eur. J. Org. Chem.* **2003**, 611.

(3) (a) Katayama, H.; Urushima, H.; Nishioka, T.; Wada, C.; Nagao, M.; Ozawa, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4513. (b) Katayama, H.; Nagao, M.; Ozawa, F. *Organometallics* **2003**, *22*, 586.

(4) Katayama, Ozawa and co-workers have reported low yields of ROCM products when vinyl ethers were used, see ref 3. Grubbs and Diver have reported related results in the cross metathesis area, see: (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (b) Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793.

(5) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153.

(6) (a) Maynard, H. D.; Grubbs, R. H. *Macromolecules* **1999**, *32*, 6917. (b) Gordon, E. J.; Geswicki, J. E.; Strong, L. E.; Kiessling, L. L. *Chem. Biol.* **2000**, *7*, 9.

(7) Weeresakare, W. M.; Liu, Z.; Rainier, J. D. *Org. Lett.* **2004**, *6*, 1625.

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

With the aforementioned in mind, we examined the ROCM reaction of 2-tosyl-7-oxanorbornene **1** with electron-rich olefins in the presence of the Grubbs 2 catalyst (Table 1). In addition to the aforementioned reaction with vinyl

**Table 1.**

entry	catalyst	X	time	furan	<i>E:Z</i> <sup>a</sup>	yield
1	<b>3</b>	OAc	1 h	<b>4</b>	1:1	61%
2	<b>3</b>		20 h	<b>5</b>	1:0	62%
3	<b>3</b>	OEt	4 h	<b>6</b>	1.2:1	94%
4	<b>2</b>	OEt	20 h	<b>6</b>	-----	-----
5	<b>3</b>	SPh	1 h	<b>7</b>	2.2:1	84%

<sup>a</sup> isolated

**2**

**3**

acetate (entry 1), we found enamides to be substrates for ROCM; the coupling of **1** with vinyl pyrrolidinone gave **5** in 62% yield as a single detectable regio- and stereoisomer (entry 2).<sup>9</sup> In addition to demonstrating the viability of electron-rich olefins other than vinyl acetate in the ROCM reaction with **1**, this transformation demonstrates what appears to be a general phenomenon: 2-sulfonylnorbornenes undergo highly regioselective ROCM reactions to give products having the internal olefin proximal to the 2-substituent.<sup>10,11</sup> To the best of our knowledge there are only two other examples, one of which was published by us, of highly regioselective unsymmetrical norbornene ROCM reactions.<sup>12,13</sup>

Interestingly, both ethyl vinyl ether and phenyl vinyl sulfide also underwent the ROCM coupling reaction with **1**

to give **6** and **7** in 94 and 84% yield, respectively (Table 1, entries 3 and 5).<sup>4</sup> As with the reaction to **4**, **6** and **7** were obtained as mixtures of olefin isomers but as a single detectable regioisomer having the electron-rich olefin proximal to the tosyl group.<sup>14</sup> It appears that the precatalyst used in these transformations is important; in our hands, the ROCM reaction of **1** and ethyl vinyl ether did not proceed with the first-generation Grubbs' catalyst **2** (Table 1, entry 4).

In the presence of **3**, 7-azanorbornene **8** also underwent regioselective ROCM reactions with electron-rich olefins (Table 2). The reactions of vinyl acetate, ethyl vinyl ether, and phenyl vinyl sulfide gave **9**, **10**, and **11** in 64, 63, and 91% yields, respectively.

**Table 2.**

entry	X	time	pyrrolidine	<i>E:Z</i> <sup>a</sup>	yield
1	OAc	20 h	<b>9</b>	1:1	64%
2	OEt	1 h	<b>10</b>	1.3:1	63%
3	SPh	3 h	<b>11</b>	6.9:1	91%

We have also found that groups other than tosyl at C(2) can influence this process (Table 3). Namely, 7-oxa-

**Table 3.**

R	norbornene	time	<i>E:Z</i> <sup>a</sup>	furan	yield
CO <sub>2</sub> Et	<b>12</b>	3 h	1:1	<b>14</b>	68%
CH <sub>2</sub> OBn	<b>13</b>	3 h	1.1:1	<b>15</b>	65%
isolated <sup>a</sup>					

norbornenes **12** and **13** having C(2) ester and C(2) alkoxy methyl substitution, respectively, underwent regioselective ROCM reactions with ethyl vinyl ether when subjected to **3** (6 mol %). Although the yields for these transformations were slightly lower than they were when **1** was subjected to ROCM with ethyl vinyl ether, the only products that we isolated had the enol ether adjacent to the substituent from the oxanorbornene.

Equally interesting was the ROCM reaction of readily available tetracycle **16**.<sup>15</sup> We were pleased to find that only

(9) Regioselectivity of all ROCM products were determined using two-dimensional NMR experiments (COSY) at either 300 or 500 MHz. See Supporting Information.

(10) At the beginning of our efforts in this area, the state of the art with regard to regioselectivity was Arjona and Plumet's use of 2-substituted 7-oxanorbornenes to give ca. 4:1 mixtures of tetrahydrofuran regioisomers. See: Arjona, O.; Csáky, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 9739.

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

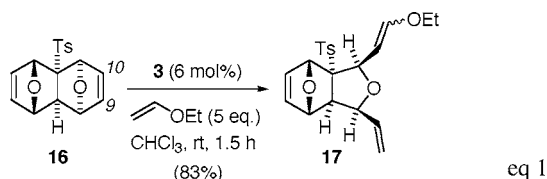
(12) Ishikura's lab has reported the regioselective coupling of 2-azanorbornenes with allylsilanes using both of the Grubbs' catalysts. See: (a) Ishikura, M.; Hasunuma, M.; Saijo, M. *Heterocycles* **2004**, *63*, 5. (b) Schneider, M. F.; Lucas, N.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 257.

(13) Other examples of regioselective ROM/CM reactions include Snapper's cyclobutene ROM/CM chemistry; 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.

(14) On the basis of previous work in ROCM chemistry, the generation of a mixture of alkene isomers is not surprising. See refs 1–4 and 7.

(15) Available from the Diels–Alder cycloaddition of furan with tosylacetylene. See: Arjona, O.; Iradier, Medel, R.; Plumet, J. *Heterocycles* **1999**, *50*, 653.

one of the two olefins in **16** underwent reaction when exposed to **3** and ethyl vinyl ether to give **17** as a single regioisomer in 83% yield (eq 1). Interestingly, **17** comes from attack by the ruthenium alkylidene on the C(9)–C(10) alkene.<sup>16</sup>



eq 1

The structures of *E*-**17** and *Z*-**17** were initially determined spectroscopically; subsequently, these assignments were confirmed using X-ray crystallography (Figure 1).

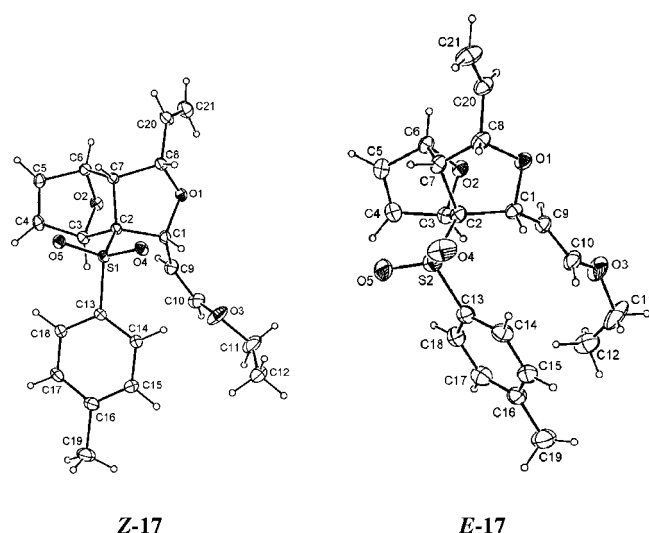


Figure 1. X-ray of *Z*- and *E*-**17**.

The regioselectivity of the substituted 7-azanorbornene ROCM reaction is dependent upon the stereochemistry of the norbornene substituent. That is, in contrast to our results with tetracycle **16** and the *exo*-tosyl isomer **18**, *exo*-tosylazanorbornene **20** reacted with ethyl vinyl ether to give a 1.3:1 ratio of **21A**:**21B** in 89% overall yield (Table 4).<sup>17,18</sup>

(16) Examination of molecular models indicates that the reactive olefin is much less sterically encumbered than the nonreactive olefin.

Table 4.

entry	X	norbornene	time	product	A:B	yield
1	O	<b>18</b>	1 h	<b>19A</b> , <sup>a</sup> <b>19B</b> <sup>a</sup>	9:1	80%
2	NBoc	<b>20</b>	1 h	<b>21A</b> , <sup>b</sup> <b>21B</b> <sup>b</sup>	1.3:1	89%

<sup>a</sup> *E*:*Z* (**19A**) = 0.9:1 (isolated), *E*:*Z* (**19B**) = 1:0 (isolated). <sup>b</sup> *E*:*Z* (**21A** and **21B**) = 1.1 (isolated).

In conclusion, we have demonstrated that electron-rich olefins undergo regioselective ROCM reactions with unsymmetrical norbornene analogues. These reactions result in the efficient and stereoselective synthesis of highly substituted furans and pyrroles having electronically distinct olefins suitable for selective manipulation. That the starting norbornenes are readily available from simple precursors makes this protocol all the more attractive. Future experiments will include the application of these reactions in the synthesis of interesting molecular targets as well as studies aimed at gaining a better understanding of the underlying features leading to regioselectivity.

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**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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(17) Use of 1-octene also gives a mixture of regioisomers. See ref 7.

(18) Goddard, Tam, and co-workers have reported regioselective oxymercurations of unsymmetrical norbornenes and have attributed the regioselectivity to the polarization of the olefin by the remote substituent. Although further work is needed, we currently believe that our results arise from a related phenomenon and the intermediacy of Fischer carbenes. The regioselectivity is the result of *exo* attack of the Fischer carbene on the polarized alkene. See: Mayo, P.; Orlova, G.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5182.