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Ring Closing Metathesis Reactions on a Phosphonate Template

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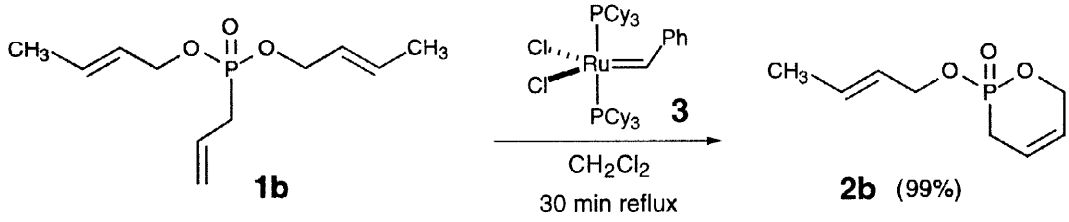
Abstract: *The first examples of ring-closing metathesis reactions on a phosphonate template catalyzed by the ruthenium alkylidene 3 are described. The yield, rate, and mode of cyclization in these reactions are sensitive to simple olefin substitution. The highlight of this method is the efficient syntheses of 2-alkyloxy-3,6-dihydro-[1,2]oxaphosphinine 2-oxide heterocycles (2).*

The ring closing metathesis reaction (RCM)[1] has emerged as a powerful approach for the construction of complex organic molecules. Recently it has been shown that the ruthenium based catalysts are tolerant to a number of functional groups including esters, amides, ammonium salts,[2] silyl ethers,[3] and α-(alkoxyalkyl)-stannane-substituted dienes.[4] In addition, the more sensitive, but more reactive molybdenum catalysts,[5] have been shown to be effective for the RCM reaction of sulfides[6] as well as for highly substituted olefins.[7] To date, the literature contains a single example of a RCM reaction on a phosphorus (phosphine)[8] based template using a tungsten carbene. As part of our program aimed at developing organometallic approaches[9] to diverse phosphorus containing compounds, we herein report the first example of a RCM reaction on phosphonate templates **1** using the ruthenium catalyst **3** to derive the cyclic allylic phosphonates **2** (Scheme 1).[10]

Scheme 1



Phosphorus containing compounds have gained considerable attention due to their diverse biological profiles.[11] Cyclic allylic phosphonates such as **2b** have enormous potential in the development of novel phosphonates, phosphonic acids, phosphinates,[12] phosphonosugars,[13] and conformationally restricted phosphonic acids.[14] One particularly attractive route to cyclic phosphonates is via the RCM reaction of diallyl allylphosphonate esters such as **1b**.

The syntheses of the phosphonate esters **1a-1i** are outlined in Scheme 2. Mild deprotection of **4**[15] with TMSCl[16] produces the phosphonic acids **5** in quantitative yield. Formation of the phosphonyl dichlorides, and subsequent esterification in toluene,[17] produces the phosphonate esters in good (**1a-1e**, 70-80%) to modest (**1f-1i**, 40-50%) yield.

The results of our metathesis studies using the ruthenium alkylidene catalyst **3** are shown in Tables 1 and 2. Initial studies on the metathesis reaction of diallyl allylphosphonate (**1a**) using benzene as solvent (reflux, 24 h) gave a modest yield of **2a** (39%) along with unreacted starting material. Changing the solvent to CH_2Cl_2 increased the rate of the reaction and improved the yield of **2a** (74%, Table 1). The RCM reaction of the dicrotyl allylphosphonate (**1b**) gave product **2b**[18] in nearly quantitative yield, indicating that substitution

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may prevent loss of product due to further reaction of the unreacted allyloxy group. Metathesis of the dihomoallyl allylphosphonate (**1c**) and diallyl homoallylphosphonate (**1d**) also occurred in good yields (74-75%) to give the seven-membered cyclic phosphonates **2c** and **2d**, respectively.

Scheme 2

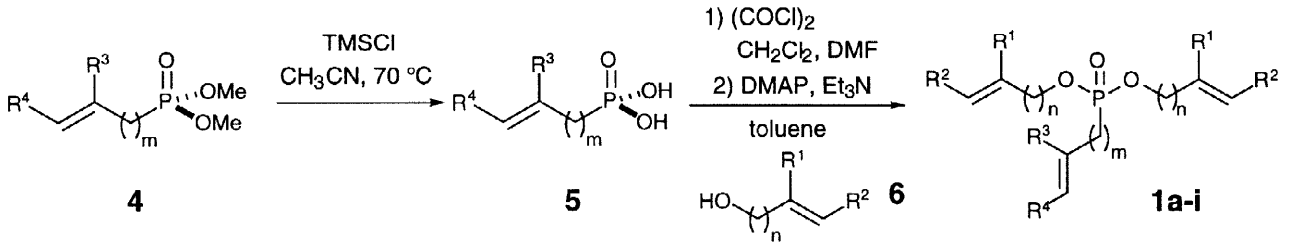
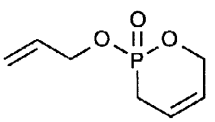
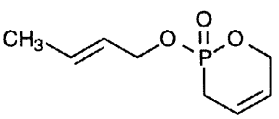
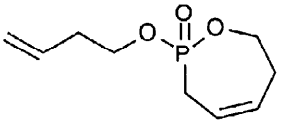
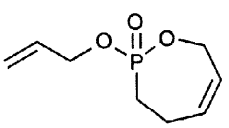


Table 1. RCM on Substrates **1a-1d**.

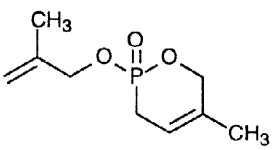
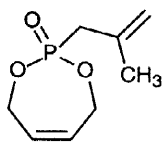
Substrate	R^1	R^2	R^3	R^4	Conditions[a]	Product	Yield
1a n, m = 1	H	H	H	H	CH_2Cl_2, 30 min reflux or 6h RT, 3 mol% **3**	 **2a**	74%
1b n, m = 1	H	CH_3	H	H	CH_2Cl_2, 30 min reflux, 3 mol% **3**	 **2b**	99%
1c m = 1, n = 2	H	H	H	H	CH_2Cl_2, 8h RT, 3 mol% **3**	 **2c**	74%
1d m = 2, n = 1	H	H	H	H	CH_2Cl_2, 30 min reflux, 3 mol% **3**	 **2d**	**75%**

a) substrate concentrations 0.01-0.02 M.

The RCM reaction of dimethallyl allylphosphonate (**1e,** Table 2) was sluggish giving a moderate yield of **2e** (52%) along with the dimer **7** (30%) (Scheme 3). In contrast to all other substrates, treatment of dicrotyl methallylphosphonate (**1f**) with catalyst **3** led to the metathesis reaction of the two crotyloxy groups producing the seven-membered cyclic phosphonate **8** in 68% yield.

It is worth noting that the reaction of substrate **1f** is the only case in which metathesis occurs between the two allyloxy groups. In all other examples, metathesis occurs exclusively between the allylphosphonate and either of the two allyloxy groups. Arguably, a preference for the formation of a six over a seven-membered ring could explain these results. However, the reaction of the substrate **1d**, in which both modes of cyclization can lead to seven membered ring formation, gave only the product of reaction between

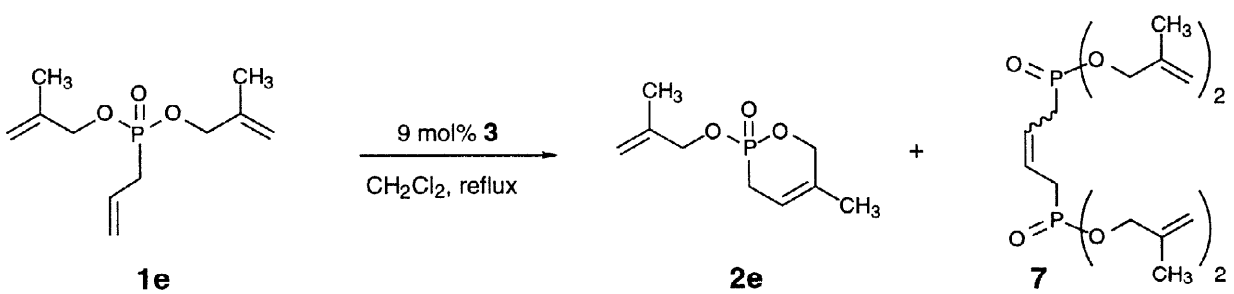
Table 2. RCM on Substrates **1e-1i** (n, m = 1).

Substrate	R^1	R^2	R^3	R^4	Conditions[a]	Product	(Yield)
1e	CH_3	H	H	H	CH_2Cl_2, 24 h reflux, 9 mol% **3**[b]	 **2e**	52% (30% dimer **7**)[c]
1f	H	CH_3	CH_3	H	CH_2Cl_2, 48 h reflux, 12 mol% **3**[b]	 **8**	68%
1g	CH_3	H	CH_3	H	CH_2Cl_2, 48 h reflux, 21 mol% **3**[b]	NR	NR
1h	H	H	H	CH_3	CH_2Cl_2, 30 min reflux, 3 mol% **3**	**2a**	78%
1i	H	CH_3	H	CH_3	CH_2Cl_2, 48 h reflux, 15 mol% **3**[b]	**2b**	68%

a) substrate concentrations 0.01-0.02 M. b) added in sequential portions of 3 mol%. c) see Scheme 3.

the homoallyl phosphonate and one of the two allyloxy groups (**2d**). Finally, the metathesis reaction of the dimethallyl methallylphosphonate (**1g**) failed. These results are in agreement with the recent studies in the Grubbs group showing that simple olefin substitution and steric effects influence not only the rate of the metathesis reaction,[7] but also the site of the initial acyclic olefin metathesis event.[19]

Scheme 3



1e **2e** **7**

Our results demonstrate the feasibility of performing RCM reactions on phosphonate templates. The rapid assembly, efficient cyclization, and the versatile nature of the resulting cyclic allylphosphonates provide an effective approach to the construction of complex phosphorus containing systems. Efforts in this direction are currently underway in this laboratory.

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15. The homoallyl substrate **4** (m = 2; R^3, R^4 = H) was synthesized by alkylation of $LiCH_2PO(OMe)_2$ with allyl bromide in THF. All of the other substrates **4** were prepared via standard Arbuzov procedures.
16. Although there are numerous methods to dealkylate phosphonate esters, we have found that mild dealkylation using TMSCl (70 °C, CH_3CN, 4 days) can cleanly produce the phosphonic acids in quantitative yield. a) Rabinowitz, R. *J. Org. Chem.* **1963**, *28*, 2975. For other methods see: b) Blackburn, G. M.; Ingleson, D. *J. Chem. Soc., Chem. Comm.* **1978**, 870. c) McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Comm.* **1979**, 739. d) Bhongle, N. N.; Notter, R. H.; Turcotte, J. G. *Synth. Comm.* **1987**, *17*, 1071.
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18. All new compounds have satisfactory ^1H, ^{13}C, and ^{31}P NMR and MS data.

    2-allyloxy-3,6-dihydro-[1,2]oxaphosphinine 2-oxide (**2b**), ^1H NMR (400 MHz, $CDCl_3$) δ 5.80-5.54 (m, 4H), 4.90-4.71 (m, 2H), 4.49-4.45 (m, 2H), 2.55-2.33 (m, 2H), 1.67 (d, J = 6.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 131.4, 125.6 (J_{CP} = 5.7 Hz), 125.0 (J_{CP} = 17.3 Hz), 120.3 (J_{CP} = 10.0 Hz), 68.7 (J_{CP} = 7.7 Hz), 65.6 (J_{CP} = 6.2 Hz), 22.3 (J_{CP} = 133.1 Hz), 17.5. ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 20.93. LRMS (CI, NH_3) 189 [MH^+].
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