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# Ring-Closing Metathesis Strategy to P-Heterocycles

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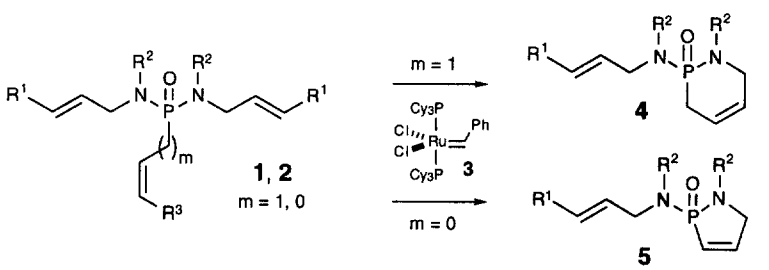
**Abstract:** The first examples of ring-closing metathesis reactions with allylphosphonamides **1**, vinylphosphonamides **2**, and vinylphosphonates **8** using the Grubbs ruthenium catalyst **3** are described. These RCM reactions lead to the 6-membered allylphosphonamides **4**, the 5-membered vinylphosphonamides **5**, and various 5-, 6- and 7-membered phosphonates **9-10**. The yield, rate and mode of metathesis in these reactions are sensitive to simple olefin and nitrogen substitution. 

The ring-closing metathesis (RCM)[1] reaction continues to emerge as a powerful approach for the construction of complex organic molecules. The Grubbs and Schrock catalysts are the most prevalent catalysts used in organic synthesis.[2] A review has appeared in the literature which thoroughly categorizes the tolerance of both the Schrock and Grubbs catalysts to a vast array of functional groups.[3] Recently we have shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst **3** is an effective method for the construction of cyclic allyl phosphonates (P-heterocycles).[4] In the literature, there is only one other example for a RCM reaction on a phosphorus containing compound (phosphine) using the Basset tungsten carbene complex.[5] As part of our program aimed at developing organometallic approaches[6] to diverse phosphorus containing compounds, we herein report examples of RCM reactions on diallyl allylphosphonamides **1**, diallyl vinylphosphonamides **2** (Scheme 1), and diallyl vinylphosphonates **8** (Scheme 2) using the ruthenium catalyst **3** to derive the P-heterocycles **4-5** and **9-10** (Tables 1-3).

**Scheme 1**




Phosphorus containing compounds have gained considerable attention due to their diverse biological profiles.[7] One particularly attractive route to phosphonamide and phosphonate heterocycles is via the RCM reaction of allyl and vinylphosphonamides such as **1-2** or vinylphosphonates **8**. The syntheses of the starting substrates **1**, **2**, and **8** are outlined in Scheme 2. Phosphonodichloridate formation from the corresponding allyl or vinylphosphonic acid[8] **6** and subsequent treatment with the corresponding amine[9] or alcohol in toluene,[10] produced the desired products in good to modest yields (**1** and **8**, 52-82%; **2**, 32-60%).

The results of our RCM studies on allylphosphonamides **1** are shown in Table 1. The RCM reaction of the N-methyl substituted allylphosphonamides **1a,c** gave excellent yields of the six membered products **4a,c**.[11] The reactions with substrates containing free N-H groups were sluggish and required higher amounts of catalyst, giving moderate yields of the products **4b,d** (45-48%). These results are in agreement with the observations of others who have found that cyclization in the presence of a free allylic amide N-H group is problematic.[12]

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**Scheme 2**

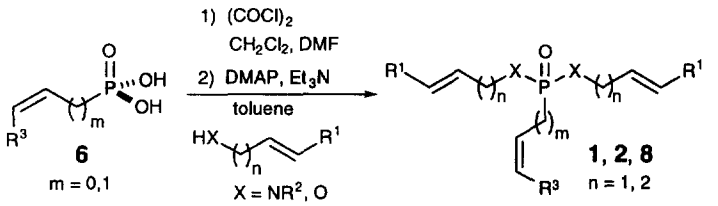
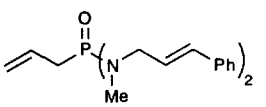
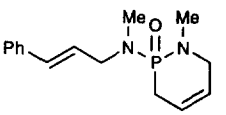
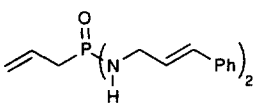
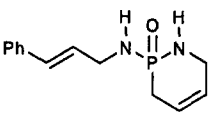
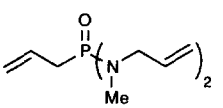
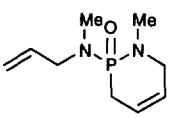
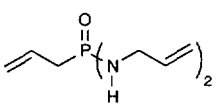
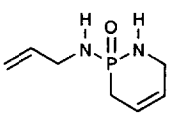



**Table 1.** RCM on Substrates **1a-d**.

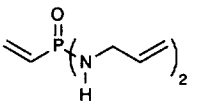
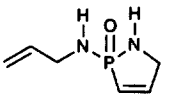
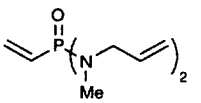
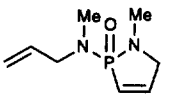
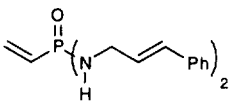
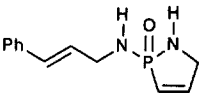
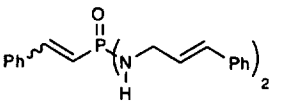
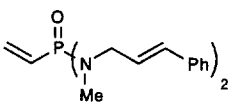
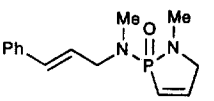
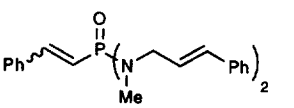
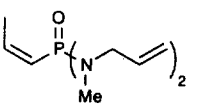
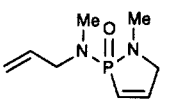
| | Substrate | Conditions[a] | Product | |
|---|---|---|---|---|
| **1a** |  | 1.5 h reflux, 3 mol% **3** | **4a**, 99% |  |
| **1b** |  | 48 h reflux, 18 mol% **3**[b] | **4b**, 48% |  |
| **1c** |  | 2 h reflux, 3 mol% **3** | **4c**, 93% |  |
| **1d** |  | 48 h reflux, 21 mol% **3**[b] | **4d**, 45% |  |

a) substrate concentrations 0.01 M in $CH_2Cl_2$. b) added in sequential portions of 3 mol%.

The RCM reactions of both N-H and N-Me vinylphosphonamides[13] **2** gave good yields of the five membered vinylphosphonamides **5** (Table 2).[14] The only low yielding reaction occurred with phosphonamide **2d** ($R^1$ = Ph, $R^2$ = Me, Table 2). Substitution on the allylamino-double bond ($R^1$ = Ph) may force the initial metathesis event to occur at the sterically-congested and electron deficient vinyl double bond, thus slowing the reactions of **2c,d**. For substrate **2d**, nitrogen substitution places additional steric constraints on the vinyl double bond as well as the bicyclo[3.2.0]metallacyclobutane intermediate.

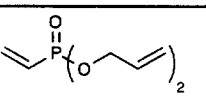
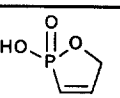
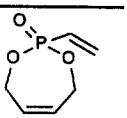
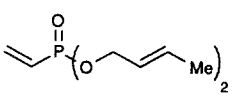
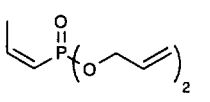
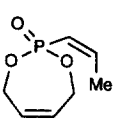
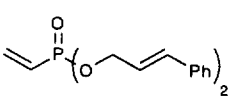
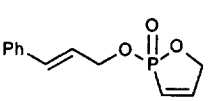
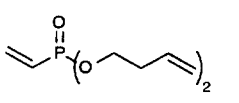
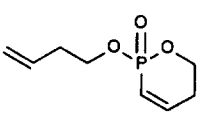
Unlike our previous results with allylphosphonates,[4] the RCM of the vinylphosphonates **8a-c** gave mixtures of the desired product **9a** and the products of metathesis between the two allyloxy groups **10a** and **10c** (Table 3). The ratio between these two products depends on the substitution pattern at the vinyl ($R^3$) and the allyloxy groups ($R^1$), which is in agreement with our earlier results and those reported by Grubbs.[15] The metathesis of phosphonate **8a** shows that there is only a slight preference for the formation of a five over a seven membered ring (44% **9a**, 31% **10a**). This result may be due to the increased strain in the five membered ring as evident by the formation of product **9a**, resulting from hydrolysis on silica gel of the initially formed metathesis product (i.e., release of ring strain). It is interesting to note that the metathesis of **8d** gave only product **9d** in low yield, and long reaction time, indicating again that substitution may force the initial metathesis event to occur at the vinyl position, thus slowing the reaction. Attempts to improve the yields of the desired product using additives such as LiCl, $MgCl_2$, or $Ti(O^iPr)_4$[1g] were unsuccessful. Finally, the metathesis of substrate **8e** gave only the six-membered phosphonate **9e** in 79% yield.

**Table 2.** RCM on Substrates **2a-e**.

| | Substrate | Conditions[a] | Product(s) | |
|---|---|---|---|---|
| **2a** |  | 6 h reflux, 9 mol% **3**[b] | **5a**, 74% |  |
| **2b** |  | 5 h reflux, 3 mol% **3** | **5b**, 76% |  |
| **2c** |  | 24 h reflux, 9 mol% **3**[b] |  **5c**, 68% |  **7c**, 17% |
| **2d** |  | 7 d reflux, 21 mol% **3**[b] |  **5d**, 13% (SM, 60%) |  **7d**, 12% |
| **2e** |  | 2 h reflux, 3 mol% **3** | **5b**, 87% |  |

a) substrate concentrations 0.01 M in $CH_2Cl_2$. b) added in sequential portions of 3 mol%.

**Table 3.** RCM on Substrates **8a-e**.

| | Substrate | Conditions[a] | Product(s) | | |
|---|---|---|---|---|---|
| **8a** |  | 6 h reflux, 6 mol% **3**[b] | **9a**, 44%[c]  | **10a**, 31% |  |
| **8b** |  | 4 d reflux, 18 mol% **3**[b] | **9a**, 54%[c] | **10a**, 6% | |
| **8c** |  | 7 h reflux, 6 mol% **3**[b] | **9a**, 16%[c] | **10c**, 54% |  |
| **8d** |  | 7 d reflux, 21 mol% **3**[b] | **9d**, 30%  | 56% SM | |
| **8e** |  | 2 h reflux, 3 mol% **3** | **9e**, 79%  | | |

a) substrate concentrations 0.01 M in $CH_2Cl_2$. b) added in sequential portions of 3 mol%. c) cleavage of the allyloxy group occurred during chromatographic purification on silica gel.

Our results demonstrate the feasibility of performing RCM reactions on allyl and vinylphosphonamide and vinylphosphonate templates. The rapid assembly, efficient cyclization, and the versatile nature of the resulting P-heterocycles provide ample entry to the construction of complex phosphorus containing systems. Further studies in these directions are currently underway in this laboratory.

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**References and Notes:**

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2. For a recent review see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
3. Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.
4. Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1998**, *39*, 3939.
5. Leconte, M.; Jourdan, I.; Pagano, S.; Lefebvre, F.; Basset, J.-M. *J. Chem. Soc., Chem. Comm.* **1995**, 857.
6. a) See reference 4. b) Hanson, P. R.; Sprott, K. T.; Wrobleski, A. D. *Tetrahedron Lett.* **1999**, *40*, 1455.
7. a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, and Silicon* **1991**, *63*, 193. b) Engel, R. *Handbook of Organophosphorus Chemistry*; Marcel Dekker, Inc.: New York, **1992**. c) Franz, J. E.; Mao, M. K.; Sikorski, J. A. *Glyphosate: A Unique Global Herbicide*; American Chemical Society: Washington, D. C., **1997**. d) Mader, M. M.; Bartlett, P. A. *Chem. Rev.* **1997**, *97*, 1281.
8. a) For the preparation of allylphosphonic acid see reference 4. b) Vinylphosphonic acid is commercially available from Sigma-Aldrich. c) For the synthesis of propenyl-phosphonates see: Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595.
9. Conditions described for the reaction of phosphonomonochloridates with amines were used for the preparation of the secondary phosphonamides: Hirschmann, R.; Yager, K. M.; Taylor, C. M.; Witherington, J.; Sprengler, P. A.; Phillips, B. W.; Moore, W.; Smith, A. B. III *J. Am. Chem. Soc.* **1997**, *119*, 8177.
10. Toluene was used as a solvent to avoid isomerization of the allyl bond in the allylphosphonic acid derivatives: Denmark, S. E.; Kim, J.-H. *J. Org. Chem.* **1995**, *60*, 7535.
11. Spectral data for **1c**: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.71-5.54 (m, 3H), 5.09 (dd, $J$ = 17.1, 1.5 Hz, 1H), 5.05 (d, $J$ = 9.8 Hz, 1H), 3.73-3.45 (m, 4H), 2.52 (d, $J$ = 9.7 Hz, 3H), 2.48 (d, $J$ =9.3 Hz, 3H), 2.41-2.35 (m, 2H). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 134.8 (d, $J_{CP}$ = 3.1 Hz), 125.3 ($J_{CP}$ = 14.7 Hz), 120.6 ($J_{CP}$ = 9.1 Hz), 116.9, 52.6, 50.8 ($J_{CP}$ = 4.6 Hz), 33.2, 32.5 ($J_{CP}$ = 4.1 Hz), 24.5 ($J_{CP}$ = 112.2 Hz). $^{31}$P NMR (161.9 MHz, $CDCl_3$) δ 25.41.
12. a) Huwe, C. M.; Kiehl, O. C.; Blechert, S. *Synlett* **1996**, 65.
13. For examples of RCM reactions of *N*-allyl acrylamides see: references 1d and 12.
14. Spectral data for **5b**: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, $J$ = 39.3, 8.8 Hz, 1H), 5.89 (dd, $J$ = 28.9, 8.8 Hz, 1H), 5.71-5.61 (m, 1H), 5.10-5.04 (m, 2H), 3.70 (dd, $J$ = 17.2, 2.2 Hz, 1H), 3.58-3.45 (m, 3H), 2.62 (d, $J$ = 7.6 Hz, 3H), 2.41 (d, $J$ = 9.9 Hz, 3H). $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 143.0 (d, $J_{CP}$ = 14.0 Hz), 135.2 ($J_{CP}$ = 2.4 Hz), 121.2 ($J_{CP}$ = 146.2 Hz), 116.6, 54.2 ($J_{CP}$ = 28.1 Hz), 51.1 ($J_{CP}$ = 5.2 Hz), 32.4 ($J_{CP}$ = 6.1 Hz), 28.8 ($J_{CP}$ = 4.9 Hz). $^{31}$P NMR (161.9 MHz, $CDCl_3$) δ 39.74.
15. a) See reference 4. b) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.