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Diastereotopic Differentiation on Phosphorus Templates via the Ring-Closing Metathesis Reaction

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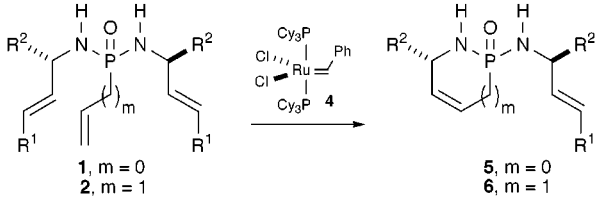
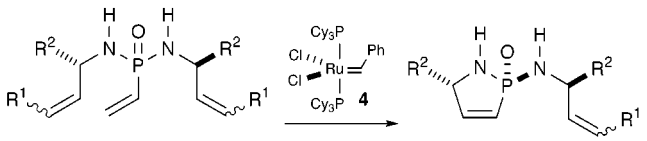
ABSTRACT



A strategy is described in which the ring-closing metathesis reaction is utilized to desymmetrize a number of pseudo-C_2-symmetric phosphorus templates 1–3. These reactions give excellent levels of selectivity (12–15:1) with vinyl phosphonamides containing a (*E*)-Ph group on the diastereotopic olefins. This approach is being developed as an effective method of obtaining *P*-chiral phosphonamides and phosphonates.

The ring-closing metathesis (RCM) reaction[1] continues to emerge as a powerful approach for the construction of complex organic molecules. Recently, we have shown that the RCM reaction catalyzed by the Grubbs ruthenium catalyst is an effective method for the construction of phosphonate and phosphonamide *P*-heterocycles.[2] As a result of the enormous synthetic potential of the RCM reaction, the development of stereoselective RCM variants is particularly important. Blechert has shown that both ruthenium- and molybdenum-catalyzed RCM reactions can be utilized in the diastereotopic differentiation of nitrogen-containing trienes.[3] In addition, Burke and Lautens have utilized desymmetrization strategies in the synthesis of various carbocycles.[4] Recently, Grubbs[5] and Hoveyda and Schrock[6] have used chiral nonracemic molybdenum catalysts for both the kinetic resolution of racemic dienes and the enantiotopic differentiation of trienes. As part of our program aimed at developing transition metal-catalyzed approaches to diverse phosphorus-containing compounds, we herein report examples of utilizing the RCM reaction in the diastereotopic differentiation of pseudo-C_2-symmetric phosphorus templates **1**−**3**. In this work we use the ruthenium catalyst **4** to derive the *P*-chiral phosphonamides **5** and **6** and phosphonates **7** (Schemes 1 and 2, Table 1).

Scheme 1



1a,b [R^1 = (*Z*)-^{i}Pr, R^2 = Me, ^{i}Pr]
1c-e [R^1 = (*E*)-Ph, R^2 = Me, ^{i}Pr, ^{t}Bu]
1f [R^1 = (*E*)-^{i}Pr, R^2 = Me]
1g [R^1 = H, R^2 = ^{t}Bu]

5a,b [R^1 = (*Z*)-^{i}Pr, R^2 = Me, ^{i}Pr]
5c-e [R^1 = (*E*)-Ph, R^2 = Me, ^{i}Pr, ^{t}Bu]
5f [R^1 = (*E*)-^{i}Pr, R^2 = Me]
5g [R^1 = H, R^2 = ^{t}Bu]

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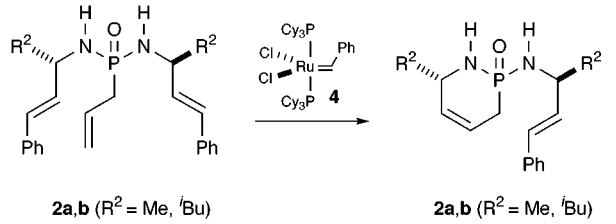
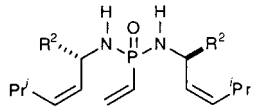
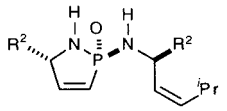
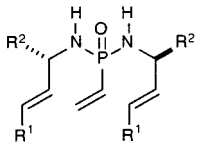
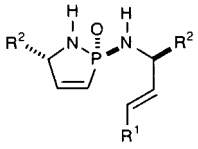
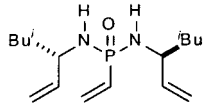
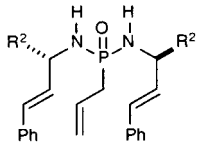
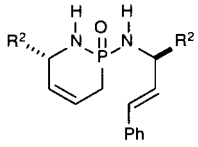
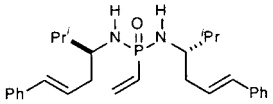
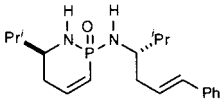
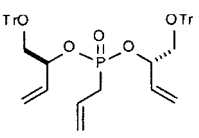
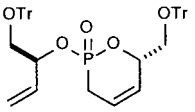
Scheme 2



Phosphorus-containing compounds have gained considerable attention as a result of their diverse biological and chemical profiles.[7] In particular, there is a growing interest in cyclic compounds containing an asymmetric phosphorus atom (*P*-chiral heterocycles).[8] An attractive route to these compounds is via a group-selective RCM reaction of nonracemic pseudo-C_2-symmetric diallyl phosphonamides and phosphonates such as **1**−**3**. The diastereotopic differentiation[9] of pseudo-C_2-symmetric molecules and the enantiotopic differentiation of achiral compounds have been previously utilized in the context of complex carbon-based natural product synthesis.[10] The implementation of this method on phosphorus templates represents a new area in the utilization of molecular symmetry to generate *P*-chiral heterocycles.

The differentiation strategy we employ requires that the initial metathesis event occurs at the central allyl or vinyl group attached to the nonstereogenic, chirotopic phosphorus

Table 1. Diastereotopic Differentiation via RCM

Substrate[a]	*ds*[b]	Isolated yield major product [%]
 **1a,b**		 **5a,b**
1a (R^2 = Me)	2.6:1	64
1b (R^2 = ^{i}Pr)	5.0:1	80
 **1c-f**		 **5c-f**
1c (R^1 = Ph, R^2 = Me)	12:1	69
1d (R^1 = Ph, R^2 = ^{i}Pr)	15:1	66
1e (R^1 = Ph, R^2 = ^{t}Bu)	15:1	63
1f (R^1 = ^{i}Pr, R^2 = Me)	3.9:1	61
 **1 g**	2.3:1	37
 **2a,b**		 **6a,b**
2a (R^2 = Me)	1.3:1	50
2b (R^2 = ^{t}Bu)	1.8:1	51
 **2 c**	1.1:1	 **6c** (42)
 **3**	3.4:1	 **7** (75)

[a] Substrate concentrations 0.01 M in CH_2Cl_2. [b] The diastereoselectivity was determined by the ^{31}P NMR spectra of the crude mixtures.

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atom. It has been shown that metathesis can be significantly slowed by steric effects.[1e,3] Our previous RCM results with simple achiral phosphonate and phosphonamide trienes indicate that proper substitution on the allyloxy- or allylamino-olefins can force the metathesis event to start at the central allyl or vinyl olefin.[2a,b] In addition, the presence of allylic branching has previously been shown by Fürstner and Burke to slow metathesis.[11] In this report, we describe our RCM results with phosphonamides containing differential substitution at both olefinic (R^1) and allylic (R^2) positions.

The starting phosphonamides and esters **1**−**3** were prepared by treatment of vinyl- or allylphosphonic dichloride with the corresponding optically pure allylic amine or alcohol in toluene[12] or dichloromethane in the presence of Et_3N. Conditions described for the reaction of phosphonomonochloridates with amines were used for the preparation of the phosphonamides.[13] The optically pure allylic amine containing an (*E*)-^{i}Pr-substituted double bond was prepared using modified Julia coupling[14] of trityl-protected α-aminoaldehyde and 1-phenyl-1-*H*-tetrazol-5-yl sulfone. The homoallylamine used as starting material for **2c** was prepared following the procedure described by Evans.[15] Wittig reaction of Boc-protected α-aminoaldehydes[16] with benzyl- or isopropyltriphenylphosphonium bromide gave (*E*)-Ph- and (*Z*)-^{i}Pr-substituted allylic amines, respectively. Optically pure allylic alcohols were prepared by Wittig reaction with (*R*)-glyceraldehyde.

We initially investigated the RCM reaction of the amino acid derived (*Z*)-configured ^{i}Pr-substituted substrates **1a**,**b** (Scheme 1). Treatment of the vinylphosphonamides **1a** (R^1 = (*Z*)-^{i}Pr, R^2 = Me, Table 1) with catalyst **4** gave the five-membered cyclic products **5a** in high yields with low diastereoselectivity (2.6:1). Not surprisingly, an increase in the size of the substituent R^2 (**1b**, R^2 = ^{i}Pr) increased the selectivity (5.0:1). We were, however, surprised to find that the substitution on the double bond plays a much more prominent role in the selectivity of the transformation. Thus, changing the double bond substituent R^1 from R^1 = (*Z*)-^{i}Pr to R^1 = (*E*)-Ph resulted in a slower reaction with considerable increase in selectivity. Treatment of the vinylphosphonamides **1c**−**e** (R^1 = (*E*)-Ph, Table 1) with catalyst **4** gave the five-membered cyclic products **5c**−**e** in good yields and excellent selectivity along with a small amount of the side product **8** (Figure 1). The size of the substituent R^2 again influences

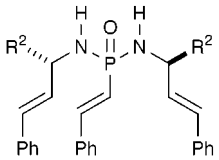

Figure 1. Side product **8**.

the diastereoselectivity, with substrate **1c** (R^2 = Me) being somewhat lower (12:1) than **1d** and **1e** (R^2 = ^{i}Pr and R^2 = ^{i}Bu, 15:1). Vinyl phosphonamides with R^1 = Ph (**1c**−**e**, **2c**) gave 13−17% of the side product **8**, which is probably due to cross-metathesis of the starting material with styrene formed as a byproduct in the reaction. Only traces of the cross-metathesis side product were formed when R^1 = ^{i}Pr, probably because of the volatile nature of the isobutylene formed.

The relative stereochemistry of compound **5c** was determined by single-crystal X-ray crystallography (Figure 2). On

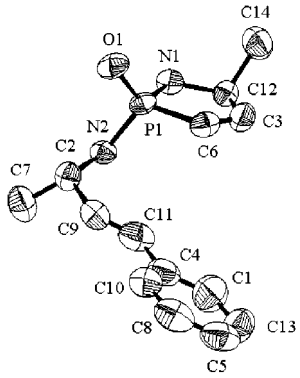

Figure 2. X-ray structure for compound **5c** (50% thermal ellipsoids; hydrogen atoms are omitted for clarity).

the basis of the chromatographic and spectroscopic behavior of compounds **5a**−**g**, it can be assumed that they all have the same relative configuration as phosphonamide **5c**.[17]

It was not clear whether the double bond configuration or the nature of the substituent R^1 on the double bond was the primary factor influencing selectivity. Therefore, we prepared compound **1f** containing the (*E*)-configured ^{i}Pr-substituted olefins. Comparison of the selectivity of the RCM of compound **1f** with **1a** and **1c** shows that the double bond geometry plays only a moderate role, while the nature of the substituent R^1 on the double bond is the dominating factor influencing selectivity. Finally, the RCM of vinylphosphonamide **1g** containing an unsubstituted double bond was very sluggish and gave product **5f** in moderate yield and low selectivity.

Formation of six-membered products from the allylphosphonamides **6a**,**b** (Scheme 2) resulted in almost complete loss of selectivity (Table 1),[18] although the yields were high. These results are in agreement with the results of Blechert

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(12) 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*, 7535−7547.

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(17) All major diastereoisomers are less polar and have lower chemical shifts in ^{31}P NMR compared to the minor diastereoisomers.

and co-workers, who reported low selectivity in the RCM reactions leading to six-membered heterocycles.[3a] Further attempts to prepare a six-membered product starting with the vinyl phosphonamide **2c** gave no selectivity.

In our efforts toward the synthesis of phosphonosugars we investigated the RCM desymmetrization of the allylphosphonate **3** (Table 1), leading to six-membered allylphosphonates **7**.[19] The RCM of **3** gave the desired six-membered product **7** in near quantitative yield with modest selectivity ranging from 3.5 to 2.8:1 depending on the reaction conditions.[20] Despite the low selectivity, we obtained the *P*-chiral cyclic phosphonate **7** in good isolated yield (75%).

In conclusion, our results demonstrate that desymmetrization via the RCM reaction is a powerful approach toward the construction of *P*-chiral five-membered heterocycles. In this investigation we have shown that the nature of the olefinic substituent is a primary factor determining the selectivity in the formation of the five-membered phosphonamides. Current efforts addressing both substrate and catalyst effects on the selectivity are underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data of new compounds, including the crystallographic data for **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The relative stereochemistry of the six-membered cyclic phosphonamides **6a**−**c** has not been unambiguously determined. The major diastereoisomers are less polar and have lower chemical shifts in ^{31}P NMR compared to the minor diastereoisomers. These trends are the same as those seen in the five-membered cyclic phosphonamides **5a**−**g**.

(19) The relative stereochemistry of the cyclic phosphonate **7** has not been unambiguously determined. Unlike the phosphonamides, the major diastereoisomers are more polar and have higher chemical shifts in ^{31}P NMR compared to the minor diastereoisomers.

(20) Substitution on the allyloxy double bond (R^1 = Ph, Me) did not improve the selectivity of the reaction.