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Diastereoselective Ring-Closing Metathesis: Synthesis of P-Stereogenic Phosphinates from Prochiral Phosphinic Acid Derivatives

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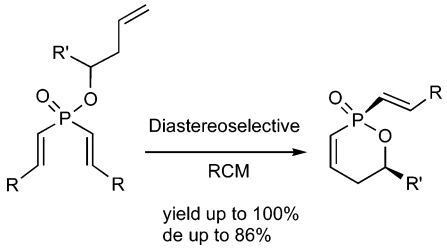

The preparation of phosphorus-containing trienes featuring two diastereotopic vinyl moieties followed by a diastereoselective ring-closing metathesis is described. This methodology allowed for the synthesis of novel highly functionalized P-stereogenic heterocycles featuring both an exo- and an endocyclic double bond. An investigation into the factors influencing the diastereochemical outcome of the ring-closing metathesis is also presented, revealing that the geometry of the double bonds conjugated to phosphorus is important and that 1,3-stereoinduction is superior to 1,4-stereoinduction for these reactions.

Introduction

Ring-closing metatheses (RCM) that use an existing stereogenic center to control the cyclization with prochiral dienes are commonly performed for the production of unsaturated carbo- and heterocycles.[1] In general, this concept of performing a diastereoselective olefin metathesis has been applied to substrates for which the olefins at the prochiral center do not react with each other and also that the primary attack of the catalyst occurs at the double bond positioned close to the stereogenic center. This process has allowed for the preparation of densely functionalized products and has been extended to highly stereoselective double-ring-closing metathesis reactions of great synthetic value. Some phosphorus heterocycles have been produced by diastereoselective ring-closing metathesis (DSRCM) as a result of their potential to serve as novel pharmaceutical, agricultural, and valuable chemicals such as chiral auxiliaries, Lewis bases, organocatalysts, or ligands used in combination with various transition metals.[2] Indeed, the diastereoselective RCM-mediated desymmetrization of nonracemic pseudo-C_2-symmetric phosphonamides and phosphonates has led to the formation of P-stereogenic heterocycles with diaster-

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(1) (a) Huwe, C. M.; Velder, J.; Blechert S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376. (b) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem.* **2000**, 3145. (c) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734. (d) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129. (e) Wallace, D. J. *Tetrahedron Lett.* **2005**, *46*, 591. (f) Wybrow, R. A. J.; Edwards, A. S.; Stevenson, N. G.; Adams, H.; Johnstone, C.; Harrity, J. P. A. *Tetrahedron* **2004**, *60*, 8869. (g) Oguri, H.; Sasaki, S.-Y.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405. (h) Fukuda, Y.-I.; Shindo, M.; Shishido, K. *Heterocycles* **2004**, *62*, 787.

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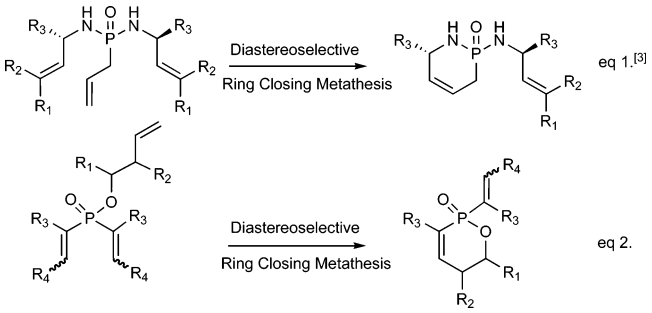
SCHEME 1. DSRCM of Phosphorus-Containing Trienes

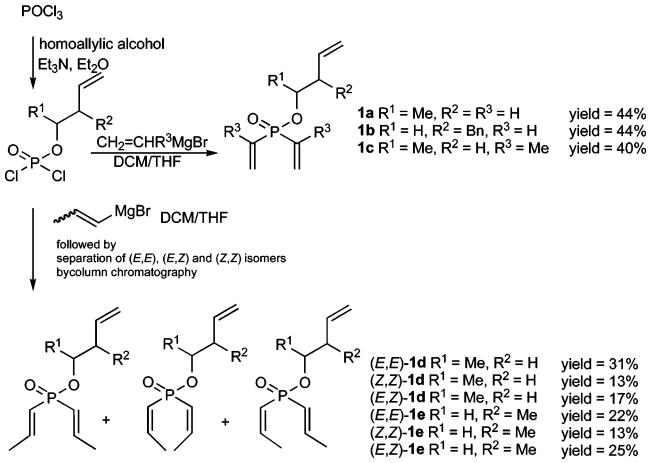


eomeric excesses ranging from 4% to 86% with the best selectivities observed for the five-membered cyclic products (Scheme 1, eq 1).[3] However, the diastereoselective ring-closing metathesis of a trienic phosphinate featuring a prochiral P-containing diene has not been studied. As part of our program aimed at the development of innovative routes to organophosphorus compounds,[4] we describe a new approach to P-stereogenic phosphinates using the DSRCM of trienic P-templates derived from homoallylic alcohols and prochiral phosphinic acids (Scheme 1, eq 2). We designed the starting trienes **1a**−**j** because the olefins at the prochiral center cannot react with each other and the primary attack of the catalyst should occur at the double bond positioned close to the stereogenic carbon ensuring diastereocontrol. Upon ring closure, the resulting products feature both an exo- and an endocyclic double bond offering the possibility for further orthogonal functional group manipulations. These products can be regarded as valuable precursors of acyclic P-stereogenic phosphine oxides upon ring opening in the presence of a carbon nucleophile. This unprecedented and concise approach to elaborated cyclic P-stereogenic phosphinates is characterized by its simplicity and high practicability. In contrast to the RCM-mediated desymmetrization of pseudo-C_2-symmetric phosphonamides, which could not deliver the six-membered allylphosphonamides with high diastereomeric excesses (ds ca. 2:1),[3] the strategy described herein uses substrates for which the primary attack of the catalyst can occur preferentially on the alkene close to the stereogenic center as the two identical double bonds are conjugated with the electron-withdrawing phosphinate. This approach delivered P-stereogenic six-membered heterocycles with a high level of diastereocontrol.

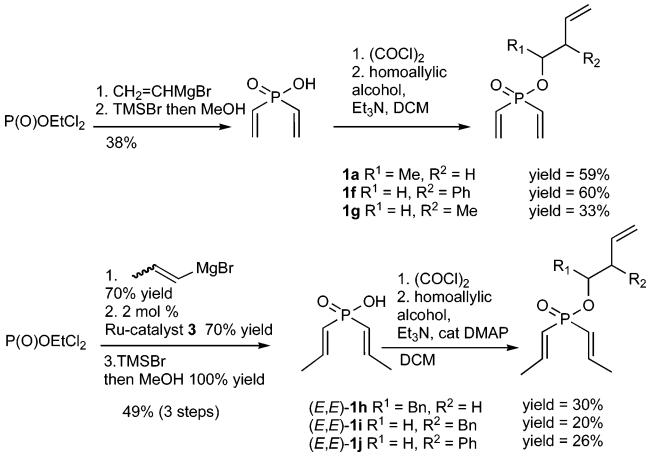
Results and Discussion

Synthesis of Phosphinate Trienes. Our investigation began with an effort to define a convergent synthetic route to trienes **1a**−**j** derived from homoallylic alcohols[5] and prochiral phosphinic acids. To study the effect of both the substitution pattern of the identical double bonds attached to the phosphorus atom and the homoallylic alcohol on the level of diastereocontrol for the RCM, we examined two complementary approaches toward trienes

SCHEME 2. Synthesis of Trienes 1a−e from $POCl_3$



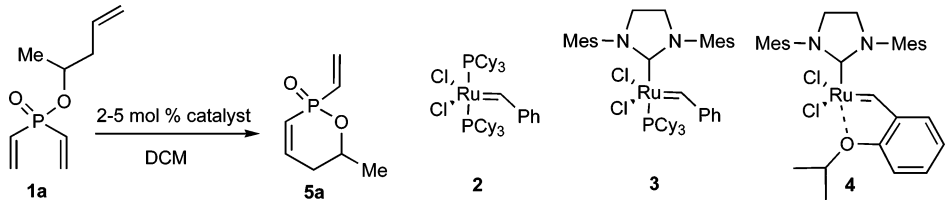
SCHEME 3. Synthesis of Trienes 1a−j from Dienic Phosphinic Acids



1a−**j** using readily accessible starting materials (Schemes 2 and 3). The first route is a two-step process using phosphorus oxychloride, various homoallylic alcohols, and commercially available alkenyl Grignard reagents. The reaction of phosphorus oxychloride with various homoallylic alcohols was carried out in the presence of triethylamine in ether to give the corresponding dichlorophosphinate species, which were used, after careful removal of triethylammonium chloride, without further purification in the next step. The addition of vinylmagnesium bromide or isopropenylmagnesium bromide on these dichlorophosphinate intermediates afforded the desired trienes **1a**−**c** with overall chemical yields of approximately 40% independent of the substitution pattern of the reacting species. Several solvents were tested for this reaction, and a 1:1 mixture of dichloromethane and tetrahydrofuran proved to be most suitable.[6] When the Grignard reagent was a mixture of *Z*- and *E*-propenylmagnesium bromide, all three geometrical isomeric products were formed and were separated by column chromatography. Compounds **1d** and **1e** were prepared with overall yields of 61% and 60%, respectively. The (*Z,Z*)- and (*E,E*)-isomers were tested individually for subsequent ring-closing metathesis (Scheme 2).

(3) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769.
(4) (a) Slinn, C. A.; Redgrave, A. J.; Hind, S. L.; Edlin, C.; Nolan, S. P.; Gouverneur, V. *Org. Biomol. Chem.* **2003**, *1*, 3820. (b) Bisaro, F.; Gouverneur, V. *Tetrahedron* **2005**, *61*, 2395. (c) Schuman, M.; Trevitt, M.; Redd, A.; Gouverneur, V. *Angew. Chem., Int.* **2000**, *39*, 2491.
(5) See the Experimental Section and Supporting Information.
(6) Dichloromethane has previously been identified as a suitable solvent for Grignard addition onto dichlorophosphinates. Polniaszek, R. P.; Foster, A. L. *J. Org. Chem.* **1991**, *56*, 3137.

SCHEME 4. Diastereoselective Ring-Closing Metathesis (DSRCM) of Triene 1a



The second approach avoids the inconvenience of geometric isomer purification by allowing for the clean formation of (*E*,*E*)-products. This approach also presents the advantage of allowing for facile diversification of the homoallylic alcohol. This alternative route is based on the use of prochiral dialkenylphosphinic acids as the key intermediates. These phosphinic acids are subsequently transformed into the corresponding phosphinate trienes using a standard coupling procedure with the homoallylic alcohol.[7] Divinyl phosphinic acid[8] was prepared in a two-step sequence starting with the reaction of commercially available ethyl dichlorophosphinate with vinylmagnesium bromide. The resulting ethyl divinylphosphinate was converted into the corresponding phosphinic acid upon treatment with trimethylsilyl bromide followed by in situ methanolysis.[9] When a mixture of *Z*- and *E*-propenylmagnesium bromide was used as the Grignard reagent, ethyl dipropenylphosphinate was formed as a mixture of all geometrical isomers (ratio *EE*/*EZ*/*ZZ* = 1:3:3). This mixture was converted into the sole (*E*,*E*)-isomer in the presence of 2 mol % of the second-generation Grubbs catalyst **3**.[10] This cis−trans isomerization proceeded with a chemical yield of 70%. It is noteworthy that this cis−trans isomerization of an alkene, which takes place in the presence of catalysts for olefin metathesis has been poorly exploited in synthesis despite its high synthetic value.[11] The resulting (*E*,*E*) dipropenylphosphinic acid ethyl ester was then quantitatively converted to the corresponding phosphinic acid with TMSBr followed by methanolysis.[9] Following this procedure, the desired geometrically pure (*E*,*E*) dipropenylphosphinic acid was obtained with an overall yield of 49% from commercially available $P(O)OEtCl_2$. Six trienes **1a** and **1f**−**j** were prepared with chemical yields up to 60% by coupling these phosphinic acids with five representative homoallylic alcohols which feature their stereogenic center either on the allylic or on the homoallylic position. The coupling was performed by activating the phosphinic acids as their phosphinoyl chlorides using an excess of oxalyl chloride, followed by addition of the homoallylic alcohol in the presence of triethylamine and a catalytic amount of DMAP (Scheme 3).

Diatereoselective Ring-Closing Metathesis. We first studied the ring-closing metathesis of triene **1a** with the commercially available Ru-based catalysts **2**−**4**[10,12] (Scheme 4, Table 1). All reactions were performed in dichloromethane at room temperature and under reflux using 2 or 5 mol % of catalyst. This preliminary study revealed that all reactions took place allowing for total conversion of the starting triene **1a** into the desired P-stereogenic ring-closed product **5a**. No other product was detected in the crude mixtures. As expected, the reaction times were significantly reduced when the reactions were performed at 40 °C. We found that the products were formed in all cases with a diastereomeric excess of approximately 60% independent of the nature of the catalyst and the temperature at which the reaction was performed.

TABLE 1. Optimization Studies for the RCM of 1a into 5a

entry	catalyst	conditions	reaction time (h)	de[a] (%)
1	**2** (5 mol %)	rt	14	60
2	**2** (5 mol %)	reflux	2.5	57
3	**3** (5 mol %)	rt	3.5	58
4	**3** (2 mol %)	reflux	0.5	60
5	**4** (5 mol %)	rt	2	58
6	**4** (2 mol %)	reflux	0.5	59

[a] Diastereomeric excess determined from the ^1H NMR of the crude mixtures.

Following this preliminary study, we elected to use 2 mol % of catalyst **3** for further studies and to carry out the ring-closing metatheses of trienes **1b**−**j** in dichloromethane (0.02 M) under reflux (Table 2). The diastereomeric ratios were determined prior to purification by means of ^1H NMR spectroscopy. Under these conditions conversion of the trienes into the desired products is normally quantitative. The yields ranging from 33% to 100% refer to the amount of diastereomeric *cis* and *trans* cyclized products recovered after purification by silica gel chromatography. The results summarized in Table 2 indicate that 1,3-stereoinduction is superior to 1,4-stereoinduction. The level of diastereocontrol for trienes derived from homoallylic alcohols featuring a stereogenic center on the allylic carbon was moderate with diastereomeric excesses ranging from 13% to 50% (entries 1−6). For these 1,4-stereoinduced ring closures, the highest diastereomeric excess was observed for the methyl-substituted triene (*E*,*E*)-**1e** derived from propenylmagnesium bromide (entry 6). Lower diastereomeric excesses of 39% and 23% were obtained for the corresponding benzyl and phenyl-substituted trienes (*E*,*E*)-**1i** and (*E*,*E*)-**1j**, respectively (entries 4 and 5). The presence of a substituent on the terminal carbon of the two double bonds conjugated to the phosphinate is always advantageous as reflected in the better diastereomeric excesses observed upon ring closure of trienes **1i**, **1j**, and **1e** (entries 4−6) in comparison with the results obtained

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(8) Maier, L. *Helv. Chim. Acta* **1971**, *54*, 275.
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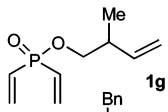
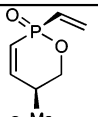
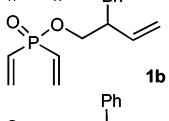
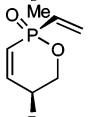
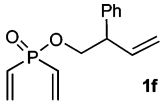
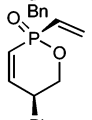
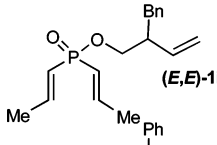
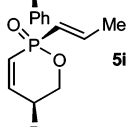
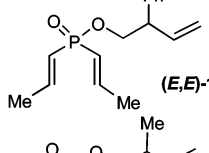
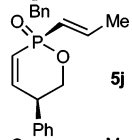
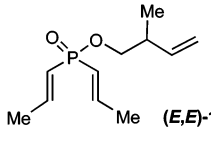
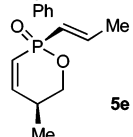
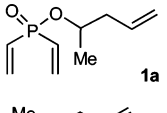
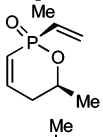
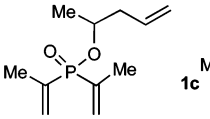
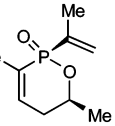
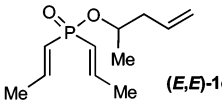
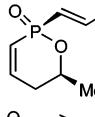
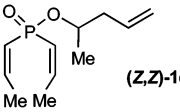
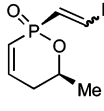
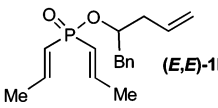
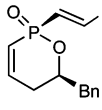
TABLE 2. DSRCM of Trienes 1a–j[a]

Entry	Substrate	Product (Major diastereomer)	yield (%)	de(%)[b]
1	 **1g**	 **5g**	72	20
2	 **1b**	 **5b**	78	19
3	 **1f**	 **5f**	60	13
4	 **(*E*,*E*)-1i**	 **5i**	56	39
5	 **(*E*,*E*)-1j**	 **5j**	61	23
6	 **(*E*,*E*)-1e**	 **5e**	92	50
7	 **1a**	 **5a**	100	60
8[c]	 **1c**	 **5c**	33[d]	76
9	 **(*E*,*E*)-1d**	 **5d**	90	86
10	 **(*Z*,*Z*)-1d**	 **5d**	95	75
11	 **(*E*,*E*)-1h**	 **5h**	97	82

[a] Triene (0.02 M in DCM), 2 mol % of **3**, reflux, 0.5 h. [b] Determined by ^{1}H NMR of the crude. [c] 4 mol % of **3**, 24 h. [d] 17% of product resulting from a self-cross-metathesis was isolated.

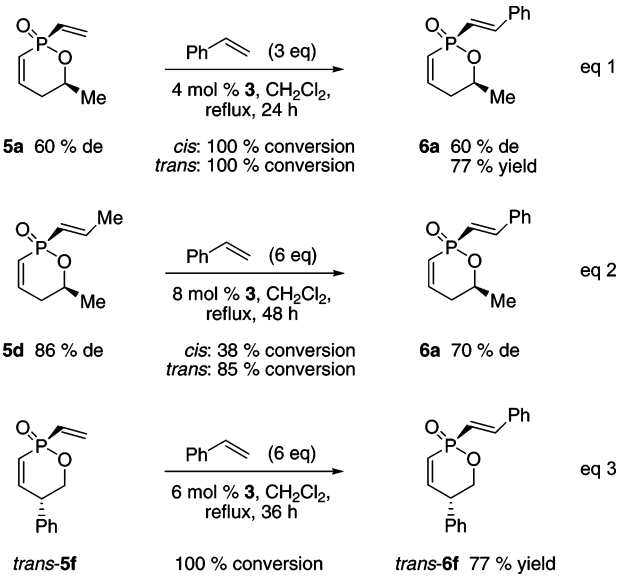
with trienes **1b**, **1f**, and **1g** (entries 1–3). This might be the result of a more favorable primary attack of the catalyst on the unsubstituted terminal double bond positioned close to the existing stereogenic center. The level of 1,3-stereoinduction was much more satisfactory (entries 7–11). For trienes derived from pent-4-en-2-ol, we studied how the substitution pattern of the two identical double bonds influences the level of diastereocontrol for the ring-closing process (entries 7–10). We found that the best diastereomeric ratio (93:7, de = 86%) was obtained for triene **1d** featuring two *E*-propenyl groups (entry 9). The corresponding triene (*Z*,*Z*)-**1d** delivered the desired product with an diastereomeric excess of 75% (entry 10). For this ring-closing metathesis, a concomitant *cis*–*trans* isomerization of the two identical double bonds took place generating a mixture of *E*/*Z* isomeric products **5d**. We also studied the reactivity of triene **1c** featuring two isopropenyl groups (entry 8). The yield of cyclized product from this triene **1c** was the lowest (33%) due to the relative difficulty of forming trisubstituted double bonds from metathesis processes. However, the diastereomeric ratio of 76% was comparable with the one obtained for the RCM of triene (*Z*,*Z*)-**1d**. For this reaction, a side product resulting from an intermolecular cross-metathesis process was isolated in 17% yield.[5] For triene **1a** possessing two vinyl groups, the diastereomeric excess dropped slightly to 60% but the yield was quantitative (entry 7). As for the 1,4-stereocontrolled ring closures, these results suggest that the trienes featuring two *E* double bonds are the best substrates for these cyclizations. Keeping this structural motif constant, we subsequently studied the level of stereocontrol that could be achieved with substrate **1h** derived from an unsaturated alcohol substituted with a benzyl group on the homoallylic position (entry 11). The cyclized product **5h** was formed in excellent yield and with a diasteromeric excess of 82%. The methyl-substituted triene **1d** having two identical *E*-configured methyl groups at the olefin termini was therefore the best substrate, allowing for the formation of the ring-closed product **5d** with an isolated overall chemical yield of 90% and a diastereomeric excess of 86%. These data allowed us to conclude that, as expected, both the substitution and the geometry of the double bonds plays a prominent role in the selectivity for these cyclizations. These reactions gave the highest diastereoselectivities to date for the preparation of six-membered P-stereogenic heterocycles using a DSRCM strategy.

Determination of Product Stereochemistry. For the cyclic phosphinates possessing their second stereogenic center β to the phosphorus atom (**5a**, **5c**, **5d**, and **5h**), separation of the two diastereomers by column chromatography proved difficult. Therefore, a chemical derivatization was performed in order to facilitate both the separation and the characterization of the two diastereomeric products (Scheme 5).

Cyclic phosphinate **5a** was subjected to cross metathesis in the presence of 3 equiv of styrene and 4 mol % of catalyst **3** to produce the styryl-substituted phosphinate **6a** in a diastereomeric ratio mirroring that of the starting material (as determined by ^{1}H NMR). The reaction was complete within 24 h in DCM at reflux. The combined yield of the two diastereomers was 77% (Scheme 5, eq 1). The identical diastereomeric excess of the substrate and product imply that no epimerization occurred upon cross metathesis. This observation corroborates previous results reported in the literature by Grela et al. who have shown that cross-metatheses of acyclic P-stereogenic vinyl phosphine oxides occur with complete retention of configuration at phosphorus.[13] Product **6a** was separated into its major and minor diastereomers by flash chromatography, allowing for full characterization. We found that compound **5d** could also be converted into **6a** but that the presence of the methyl group on the double bond resulted in a slower reaction rate. For this reaction, the

(13) Demchuk, O. M.; Pietrusiewicz, K. M.; Michrowska, A.; Grela, K. *Org. Lett.* **2003**, *5*, 3217.

SCHEME 5. Cross-Metathesis of Compounds 5a, 5d, and 5f with Styrene



minor (*trans*) diastereomer reacted faster (Scheme 5, eq 2). The relative stereochemistry of the major and minor diastereomers of compound **6a** was determined by single-crystal X-ray analysis of both isomers to be *cis* and *trans*, respectively.[5] In both cases, the atoms of the phosphinate ring are approximately coplanar, with the exception of the carbon bonded to the methyl group. In the major *cis* isomer this carbon lies syn to the P=O bond, whereas in the minor *trans* isomer it lies anti to the P=O bond. As a result, the methyl substituent occupies the equatorial position in both structures.

Qualitative NOE data for the *cis* diastereomer of **6a** suggest that, in solution, significant flexing of the phosphinate ring occurs since a weak NOE was observed between the methyl protons and the styryl proton α to phosphorus. This is despite an interproton distance in the X-ray structure of 4.71 Å, which is at the extreme limit for detecting NOEs (Figure 1). For the *trans* diastereomer of **6a**, a strong NOE was observed between the ring proton α to oxygen and the α styryl proton, which is consistent with the interproton distance of 2.6 Å in the X-ray structure. NOE experiments were also performed on diastereomeric mixtures of **5c** and **5h**, and the results were consistent with the major isomer being *cis* and the minor *trans*.

For all the compounds derived from the longer range 1,4-stereocontrol (**5b**, **5e**−**g**, **5i**, and **5j**), separation of the two diastereomers by column chromatography was possible. The minor diastereomer of cyclic phosphinate **5f** was subjected to cross-metathesis in the presence of 6 equiv of styrene and 6 mol % of catalyst **3** to produce the

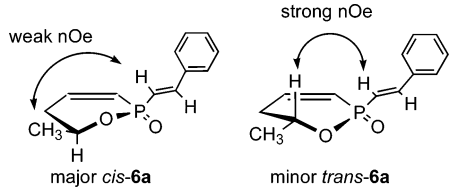


FIGURE 1. Observed NOEs for *cis* and *trans* isomers of phosphinate **6a**.

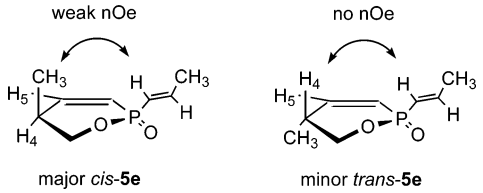


FIGURE 2. Observed NOEs for *cis* and *trans* isomers of phosphinate **5e**.

TABLE 3. *J* Couplings $^3J(H_4,H_5)$ for the 1,4-Substituted Cyclic Phosphinate Series

phosphinate	$^3J(H_4,H_5)$/Hz	phosphinate	$^3J(H_4,H_5)$/Hz
cis-**5g**	4.8	*trans*-**5g**	1.9
cis-**5b**	5.2	*trans*-**5b**	1.3
cis-**5f**	4.5	*trans*-**5f**	1.9
cis-**5i**	5.2	*trans*-**5i**	1.5
cis-**5j**	4.6	*trans*-**5j**	1.9
cis-**5e**	4.9	*trans*-**5e**	1.9
cis-**6f**	-	*trans*-**6f**	1.9

styryl derivative **6f** (Scheme 5, eq 3). Single-crystal X-ray analysis of compound **6f** confirmed it to be the *trans* diastereomer.[5] This result allows us to conclude that the 1,4-stereoinduced ring-closing metathesis reactions gave the preferential *cis*-diastereomer (entries 1−6, Table 2). The conformation of *trans*-**6f** is similar to that of *cis*-**6a**, with the methylene unit β to the phosphorus group lying syn to the P=O bond. Thus, the phenyl group attached to the adjacent carbon occupies the equatorial position.[5]

Qualitative NOE data for all of the major and minor 1,4-disubstituted phosphinates are consistent with the major isomers being *cis* and the minor *trans*. This is illustrated in Figure 2 for compound **5e**, in which a weak NOE was observed between the methyl substituent on the ring and the propenyl proton α to phosphorus in the major diastereomer but not in the minor diastereomer. An NOE in the minor diastereomer between H_4 and the α propenyl proton was not observed, which is consistent with the interproton distance of 3.88 Å in the crystal structure of the related compound **6f**.

Evidence that the methyl substituent occupies an equatorial position in the *trans* diastereomer (analogously with the phenyl substituent of *trans*-**6f**) is found by observing the small coupling constant (1.9 Hz) between H_4 and H_5, which is consistent with a dihedral angle of approximately 90°. The equivalent angle in *trans*-**6f** was measured to be 85.9°. For the *cis* diastereomer of **5e**, the coupling between H_4 and H_5 is much greater (4.9 Hz), implying a dihedral angle of approximately 30°. This observation is consistent with proton H_4 being equatorial, and hence the methyl group being axial, in this compound. This relationship was retained throughout the 1,4-substituted phosphinate series (Table 3) and could be used as a diagnostic tool to identify *cis* versus *trans* stereochemistry. A further implication of these observations is that, for this series of compounds, the *cis* and *trans* isomers have similar conformations, with the methylene unit β to phosphorus lying syn to the P=O bond. The alternative conformation, having this unit lying anti to the P=O bond, would place the substituent at position 4 in the equatorial position in the *cis* isomers leading to $A^{(1,2)}$-strain. Unfortunately, attempts to find a

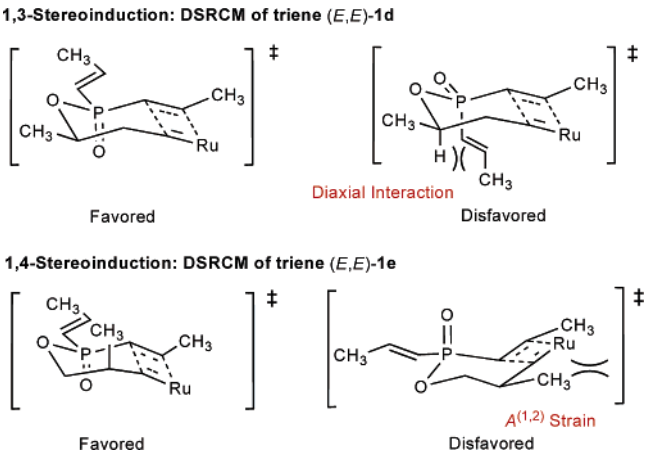


FIGURE 3. 1,3- versus 1,4-stereoinduction in diastereoselective ring-closing metathesis.

suitable *cis* 1,4-substituted compound for X-ray analysis to verify this prediction were unsuccessful.

To gain some understanding of the key DSRCM reaction, we performed additional experiments in order to determine whether the products obtained upon ring closure were the result of a kinetically or thermodynamically controlled process. After separation of the two diastereomers of product **5b**, both the major *cis* and minor *trans* isomers were subjected separately to the reaction conditions for a period of 24 h (2 mol % catalyst **3**, reflux, DCM). The experiments revealed that no epimerization took place under these conditions, suggesting that the reactions are under kinetic control. For the 1,3-stereocontrolled ring closing metathesis of triene (*E*,*E*)-**1d** operating with the best diastereomeric excess, the formation of the major *cis* isomer might be rationalized by a preferred transition state placing both substituents in equatorial positions, thus avoiding steric interactions derived from axial groups. For the 1,4-stereocontrolled ring-closing metathesis of compound (*E*,*E*)-**1e**, the methyl group positioned on the stereogenic carbon probably preferentially adopts the pseudoaxial position to prevent the $A^{(1,2)}$ strain that occurs when the methyl group adopts the pseudoequatorial position. These DSRCM reactions might therefore be consistent with a kinetic reaction preferentially delivering the more thermodynamically stable products (Figure 3).

In conclusion, we have prepared a series of novel P-stereogenic heterocycles featuring two stereogenic centers using a diastereoselective ring closing metathesis of the corresponding structurally diverse P-containing trienes. The best results were obtained for 1,3-stereocontrolled ring closures. The exo- and endocyclic double bonds of the products offer a variety of possibilities for further elaboration. Efforts to prepare acyclic homochiral P-stereogenic ligands using this DSRCM strategy followed by functional group manipulation of the resulting primary products are in progress and will be reported in due course.

Experimental Section

Synthesis of Ethyl Divinylphosphinate.[8] To a cooled solution (−78 °C) of ethyl dichlorophosphate (2 mL, 16.9 mmol) in dichloromethane (85 mL) was added vinylmagnesium bromide (34 mL of a 1.0 M solution in THF, 34.0 mmol) dropwise. The reaction mixture was stirred for 40 min at −78 °C, warmed to room temperature, and poured into icy 2 M HCl (200 mL). The aqueous phase was extracted with dichloromethane. The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (EtOAc to EtOAc/MeOH 95:5) afforded ethyl divinylphosphinate as a yellow oil: yield 950 mg (38%); R_f 0.4 (EtOAc/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04−6.31 (m, 6H; P(C*H*=CH_2)$_2$), 3.99 (dq, $^3J_{(H,P)}$ 7.1, $^3J_{(H,H)}$ 7.1 Hz, 2H; POCH_2), 1.28 ppm (dt, $^3J_{(H,H)}$ 7.1, $^4J_{(H,P)}$ 1.3 Hz, 3H; POCH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (d, $^2J_{(C,P)}$ 2.0 Hz, P(CH=*C*H$_2$)$_2$), 129.1 (d, $^1J_{(C,P)}$ 131.3 Hz, P(*C*H=CH$_2$)$_2$), 60.6 (d, $^2J_{(C,P)}$ 5.8 Hz, POCH$_2$), 16.5 ppm (d, $^3J_{(C,P)}$ 6.4 Hz, *C*H$_3$); ^{31}P NMR (101 MHz, $CDCl_3$) δ 29.6 ppm; IR (film) ν 1609 (C=C), 1209 cm^{-1} (P=O); MS (ESI) *m/z* 205 [M + CH_3CN + NH_4]$^+$.

Synthesis of Divinylphosphinic Acid.[8] To cooled ethyl divinylphosphinate (1.0 g, 8.5 mmol) (0 °C) was added bromotrimethylsilane (1.34 mL, 12.5 mmol). The mixture was stirred for 3 h at 0 °C and then warmed to room temperature, and methanol (2 mL) was added. After being stirred for 30 min, the solution was concentrated in vacuo to afford divinylphosphinic acid as a brown oil: yield 1.0 g (100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (brs, 1H; O*H*), 6.21−6.43 ppm (m, 6H; P(C*H*=CH_2)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (d, $^2J_{(C,P)}$ 1.6 Hz, P(CH=*C*H$_2$)$_2$), 127.0 ppm (d, $^1J_{(C,P)}$ 135.8 Hz, P(*C*H=CH$_2$)$_2$); ^{31}P NMR (101 MHz, $CDCl_3$) δ 35.9 ppm; MS (ESI) *m/z* 177 [M + CH_3CN + NH_4]$^+$.

General Method A for the Preparation of Phosphinates 1. To a cooled 0.7 M solution (−78 °C) of a homoallylic alcohol (1 equiv) in diethyl ether was added triethylamine (1 equiv) followed by dropwise addition of a 0.3 M solution of phosphorus oxychloride (1 equiv) in diethyl ether. The mixture was allowed to warm to room temperature while stirring overnight. After filtration under argon to remove triethylammonium salt, the solution was concentrated in vacuo at below room temperature. Dichloromethane was added to the residue to form a 0.2 M solution, which was cooled to −78 °C. A solution of Grignard reagent (2 equiv) in THF was added dropwise and the mixture stirred for 1−3 h. The mixture was then warmed to room temperature and poured into icy 2 M HCl. The aqueous phase was extracted with dichloromethane. Combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo.

General Method B for the Preparation of Phosphinates 1. To a cooled 0.2 M solution (0 °C) of a phosphinic acid (1 equiv) in dichloromethane was added dry DMF (1 drop) followed by dropwise addition of oxalyl chloride (3 equiv). The mixture was warmed to room temperature, stirred for 1 h, and then concentrated in vacuo at below room temperature. Dichloromethane was added to the residue to form a 0.25 M solution, which was cooled to −78 °C. DMAP (0.02 equiv) and triethylamine (1.1 equiv) were added followed by dropwise addition of a 1.0 M solution of an alcohol **8** (1 equiv) in dichloromethane. The mixture was warmed to room temperature, stirred for 2 h, and then concentrated in vacuo.

Pent-4-en-2-yl Divinylphosphinate 1a. Prepared by method A from pent-4-en-2-ol (0.7 mL, 7.0 mmol) and vinylmagnesium bromide (14 mL of a 1.0 M solution, 14.0 mmol) and by method B from divinylphosphinic acid (215 mg, 1.82 mmol) and 4-penten-2-ol (0.2 mL, 1.94 mmol). Purification by flash chromatography (EtOAc) afforded **1a** as a yellow oil: method A yield 580 mg (44%); method B yield 200 mg (59%); R_f 0.3 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05−6.34 (m, 6H; P(C*H*=CH_2)$_2$), 5.76 (m, 1H; CH$_2$C*H*=CH$_2$), 5.07−5.11 (m, 2H; CH$_2$CH=CH_2), 4.52 (dddq, $^3J_{(H,P)}$ 9.0, $^3J_{(H,H)}$ 6.2 Hz × 3, 1H; POC*H*), 2.36 (m, 2H; CH_2CH=CH$_2$), 1.31 ppm (d, $^3J_{(H,H)}$ 6.2 Hz, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (d, $^2J_{(C,P)}$ 1.9 Hz, P(CH=*C*H$_2$)$_A$), 134.7 (d, $^2J_{(C,P)}$ 1.9 Hz, P(CH=*C*H$_2$)$_B$), 133.4 (s, CH$_2$*C*H=CH$_2$), 129.9 (d, $^1J_{(C,P)}$ 132.3 Hz, P(*C*H=CH$_2$)$_A$), 129.7 (d, $^1J_{(C,P)}$ 131.5 Hz, P(*C*H=CH$_2$)$_B$), 118.1 (s, CH$_2$-*C*H=CH$_2$), 72.1 (d, $^2J_{(C,P)}$ 6.2 Hz, PO*C*H), 42.2 (d, $^3J_{(C,P)}$ 4.9 Hz,

$CH_2CH{=}CH_2$), 21.8 ppm (d, $^3J_{(C,P)}$ 3.0 Hz, CH_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ 28.5 ppm; IR (film) ν 1643 and 1608 (C=C), 1215 (P=O); HRMS (CI) *m/z* calcd for $C_9H_{16}O_2P$ $[M + H]^+$ 187.0888, found 187.0890.

General Procedure for the RCM of Phosphinates 1. To a 0.02 M solution of a phosphinate **1** in dichloromethane was added catalyst **3** (2 mol %). The mixture was stirred at reflux for 30 min and then concentrated in vacuo.

RCM of 1a. Phosphinate **1a** (151 mg, 0.81 mmol) underwent RCM according to the general procedure above to form cyclic phosphinate **5a** in 60% de. Purification by flash chromatography (EtOAc/MeOH 98:2 to EtOAc/MeOH 95:5) afforded **5a** as a brown oil. The diastereomers were not separated. **6-Methyl-2-vinyl-5,6-dihydro-1,2-oxaphosphorin 2-oxide 5a:** yield 132 mg (100%); R_f 0.3 (EtOAc/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (dddd, $^3J_{(H,P)}$ 37.9, $^3J_{(H,H)}$ 12.7, $^3J_{(H,H)}$ 5.5, $^3J_{(H,H)}$ 2.6 Hz, 1H; PCH=C*H*)^{trans}, 6.77 (dddd, $^3J_{(H,P)}$ 39.0, $^3J_{(H,H)}$ 12.6, $^3J_{(H,H)}$ 5.5, $^3J_{(H,H)}$ 2.4 Hz, 1H; PCH=C*H*), 6.38 (m, 1H; PCH=C$H_{cis}H_{trans}$), 5.96−6.29 (m, 3H; PC*H*=C$H_{cis}H_{trans}$ and PC*H*=CH), 4.72 (m, 1H; POC*H*), 4.46 (m, 1H; POC*H*)^{trans}, 2.32−2.46 (m, 2H; PCH=CHCH_2)^{trans}, 2.29 (m, 2H; PCH=CHCH_2), 1.42 (d, $^3J_{(H,H)}$ 6.1 Hz, 3H; CH_3)^{trans}, 1.41 ppm (dd, $^3J_{(H,H)}$ 6.1, $^4J_{(H,P)}$ 1.2 Hz, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.0 (d, $^2J_{(C,P)}$ 1.0 Hz, PCH=*C*H), 136.3 (d, $^2J_{(C,P)}$ 2.0 Hz, PCH=*C*H_2), 129.0 (d, $^1J_{(C,P)}$ 139.8 Hz, P*C*H=CH_2), 120.4 (d, $^1J_{(C,P)}$ 119.8 Hz, P*C*H=CH), 69.8 (d, $^2J_{(C,P)}$ 6.0 PO*C*H), 34.5 (d, $^3J_{(C,P)}$ 8.9 Hz, PCH=CH*C*H_2), 22.0 ppm (d, $^3J_{(C,P)}$ 7.6 Hz, *C*H_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ 25.5 (trans), 22.2 ppm (*cis*); IR (film) ν 1612 (C=C), 1217 (P=O); HRMS (CI) *m/z* calcd for $C_7H_{12}O_2P$ $[M + H]^+$ 159.0575, found 159.0571.

RCM of 1b. Phosphinate **1b** (145 mg, 0.55 mmol) underwent RCM according to the general procedure above to form cyclic phosphinate **5b** in 19% de. Purification by flash chromatography (EtOAc/MeOH 98:2 to EtOAc/MeOH 95:5) afforded the *cis* and *trans* diastereomers of **5b** as brown oils. **(2*SR*,5*SR*)-5-Benzyl-2-vinyl-5,6-dihydro-1,2-oxaphosphorin 2-oxide *cis*-5b:** yield 59 mg (45%); R_f 0.1 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.34 (m, 5H; Ar−H), 6.83 (ddd, $^3J_{(H,P)}$ 37.8, $^3J_{(H,H)}$ 12.6, $^3J_{(H,H)}$ 5.2 Hz, 1H; PCH=C*H*), 6.06−6.42 (m, 3H; PC*H*=C*H*$_2$), 6.03 (dd, $^2J_{(H,P)}$ 22.9, $^3J_{(H,H)}$ 12.6 Hz, 1H; PC*H*=CH), 4.49 (ddd, $^2J_{(H,H)}$ 11.6, $^3J_{(H,P)}$ 8.6, $^3J_{(H,H)}$ 3.3 Hz, 1H; POCH_AH_B), 4.07 (ddm, $^3J_{(H,P)}$ 17.2, $^2J_{(H,H)}$ 11.6 Hz, 1H; POCH_AH_B), 2.83 (dd, $^2J_{(H,H)}$ 13.5, $^3J_{(H,H)}$ 6.5 Hz, 1H; CH_AH_BPh), 2.72 (dd, $^2J_{(H,H)}$ 13.5, $^3J_{(H,H)}$ 8.8 Hz, 1H; CH_AH_BPh), 2.59 ppm (m, 1H; C*H*CH$_2$Ph); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.3 (s, PCH=*C*H), 138.0 (s, Ar−C_{ipso}), 136.3 (d, $^2J_{(C,P)}$ 2.7 Hz, PCH=*C*H_2), 129.0 (s, Ar−C), 128.9 (d, $^1J_{(C,P)}$ 138.3 Hz, P*C*H=CH_2), 128.7 (s, Ar−C), 126.8 (s, Ar−C_{para}), 120.0 (d, $^1J_{(C,P)}$ 119.3 Hz, P*C*H=CH), 65.5 (d, $^2J_{(C,P)}$ 6.3 PO*C*H_2), 38.6 (d, $^3J_{(C,P)}$ 9.2 Hz, *C*HCH$_2$Ph), 37.1 ppm (d, $^4J_{(C,P)}$ 2.3 Hz, *C*H_2Ph); ^{31}P NMR (101 MHz, $CDCl_3$) δ 20.5 ppm; IR (film) ν 1604 (C=C), 1219 (P=O); HRMS (CI) *m/z* calcd for $C_{13}H_{16}O_2P$ $[M + H]^+$ 235.0888, found 235.0900. **(2*SR*,5*RS*)-5-Benzyl-2-vinyl-5,6-dihydro-1,2-oxaphosphorin 2-oxide *trans*-5b:** yield 42 mg (33%); R_f 0.2 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.34 (m, 5H; Ar−H), 6.71 (dddd, $^3J_{(H,P)}$ 37.8, $^3J_{(H,H)}$ 12.6, $^4J_{(H,H)}$ 1.2 Hz × 2, 1H; PCH=C*H*), 6.34 (ddd, $^3J_{(H,P)}$ 24.2, $^3J_{(H,H)}$ 17.7, $^2J_{(H,H)}$ 2.6 Hz, PCH=C$H_{cis}H_{trans}$), 6.07−6.27 (m, 2H; PC*H*=C$H_{cis}H_{trans}$), 6.02 (ddd, $^2J_{(H,P)}$ 23.3, $^3J_{(H,H)}$ 12.7, $^4J_{(H,H)}$ 2.3 Hz, 1H; PC*H*=CH), 4.12−4.26 (m, 2H; POCH_2), 2.82 (m, 1H; C*H*CH$_2$Ph), 2.72 ppm (m, 1H; CH_2Ph); ^{13}C NMR (101 MHz, $CDCl_3$): δ 150.7 (s, PCH=*C*H), 137.6 (s, Ar−C_{ipso}), 136.3 (d, $^2J_{(C,P)}$ 2.3 Hz, PCH=*C*H_2), 128.9 (s, Ar−C), 128.8 (s, Ar−C), 128.8 (d, $^1J_{(C,P)}$ 137.8 Hz, P*C*H=CH_2), 126.9 (s, Ar−C_{para}), 120.0 (d, $^1J_{(C,P)}$ 119.1 Hz, P*C*H=CH), 67.0 (d, $^2J_{(C,P)}$ 6.4 PO*C*H_2), 38.7 (d, $^3J_{(C,P)}$ 9.3 Hz, *C*HCH$_2$Ph), 36.7 ppm (d, $^4J_{(C,P)}$ 1.3 Hz, *C*H_2Ph); ^{31}P NMR (101 MHz, $CDCl_3$) δ 21.3 ppm; IR (film) ν 1603 (C=C), 1221 (P=O); HRMS (CI) *m/z* calcd for $C_{13}H_{16}O_2P$ $[M + H]^+$ 235.0888, found 235.0894.

General Procedure for the Cross-Metathesis of Cyclic Phosphinates 5 with Styrene. To a 0.3 M solution of a cyclic phosphinate **5** (1 equiv) in dichloromethane were added styrene (3 equiv) and catalyst **3** (2 mol %). The mixture was stirred at reflux. Further portions of catalyst (2 mol %) were added at 12 h intervals, and further portions of styrene (3 equiv) were added at 24 h intervals. Upon completion of the reaction or after stirring for 48 h, the solution was concentrated in vacuo.

Cross-Metathesis of 5a with Styrene. Cyclic phosphinate **5a** (4:1 mixture of *cis* and *trans* diastereomers) (49 mg, 0.31 mmol) underwent cross-metathesis with styrene (100 μL, 0.93 mmol) in the presence of catalyst **3** (10 mg, 0.012 mmol, 4 mol %) as described in the general procedure above. After 24 h, ^{1}H NMR showed that complete conversion of both diastereomers of **5a** had occurred. Purification by flash chromatography (EtOAc to EtOAc/MeOH 98:2) afforded the *cis* and *trans* diastereomers of **6a** as white solids, which were recrystallized from toluene. **(2*RS*,6*SR*)-6-Methyl-2-(*E*)-styryl 5,6-dihydro-1,2-oxaphosphorin 2-oxide *cis*-6a:** yield 45 mg (61%); R_f 0.3 (EtOAc/MeOH 95:5); mp 126−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, $^3J_{(H,P)}$ 21.5, $^3J_{(H,H)}$ 17.5, 1H; PCH=C*H*Ph), 7.47−7.49 (m, 2H, Ar−H), 7.34−7.38 (m, 3H, Ar−H), 6.76 (dddd, $^3J_{(H,P)}$ 39.2, $^3J_{(H,H)}$ 12.5, $^3J_{(H,H)}$ 4.0 Hz × 2, 1H; PCH=C*H*CH$_2$), 6.25 (dd, $^2J_{(H,P)}$ 20.6, $^3J_{(H,H)}$ 17.5 Hz, 1H; PC*H*=CHPh), 6.06 (dd, $^2J_{(H,P)}$ 24.0, $^3J_{(H,H)}$ 12.7 Hz, 1H; PC*H*=CHCH$_2$), 4.81 (ddq, $^3J_{(H,H)}$ 6.2 Hz × 3, 1H; POC*H*), 2.26 (m, 2H; PCH=CHCH_2), 1.41 ppm (d, $^3J_{(H,H)}$ 6.2 Hz, 3H; POCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (d, $^2J_{(C,P)}$ 6.3 Hz, PCH=*C*HPh), 145.3 (s, PCH=*C*HCH$_2$), 134.9 (d, $^3J_{(C,P)}$ 20.8 Ar−C_{ipso}), 130.2 (s, Ar−C_{para}), 128.7 (s, Ar−C), 127.7 (s, Ar−C), 121.0 (d, $^1J_{(C,P)}$ 121.3 Hz, P*C*H=CHCH$_2$), 116.9 (d, $^1J_{(C,P)}$ 146.9 Hz, P*C*H=CHPh), 69.8 (d, $^2J_{(C,P)}$ 6.1 PO*C*H), 34.5 (d, $^3J_{(C,P)}$ 8.8 Hz, PCH=CH*C*H_2), 22.0 ppm (d, $^3J_{(C,P)}$ 7.6 Hz, POCH*C*H_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ 22.5 ppm; IR (film) ν 1608 (C=C), 1205 (P=O); HRMS (CI) *m/z* calcd for $C_{13}H_{16}O_2P$ $[M + H]^+$ 235.0888, found 235.0894. **(2*RS*,6*RS*)-6-Methyl-2-(*E*)-styryl-5,6-dihydro-1,2-oxaphosphorin 2-oxide *trans*-6a:** yield 12 mg (16%); R_f 0.4 (EtOAc/MeOH 95:5); mp 126−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.52 (m, 6H, Ar−H and PCH=C*H*Ph), 6.85 (dddd, $^3J_{(H,P)}$ 38.1, $^3J_{(H,H)}$ 12.6, $^3J_{(H,H)}$ 2.6, $^3J_{(H,H)}$ 1.0 Hz, 1H; PCH=C*H*CH$_2$), 6.46 (dd, $^2J_{(H,P)}$ 27.8, $^3J_{(H,H)}$ 17.8 Hz, 1H; PC*H*=CHPh), 6.09 (ddm, $^2J_{(H,P)}$ 21.1, $^3J_{(H,H)}$ 12.6 Hz, 1H; PC*H*=CHCH$_2$), 4.57 (m, 1H; POC*H*), 2.40−2.49 (m, 1H; PCH=CHCH_AH_B), 2.30−2.37 (m, 1H; PCH=CHCH_AH_B) 1.45 ppm (d, $^3J_{(H,H)}$ 6.3 Hz, 3H; POCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (d, $^2J_{(C,P)}$ 6.8 Hz, PCH=*C*HPh), 146.8 (s, PCH=*C*HCH$_2$), 134.9 (d, $^3J_{(C,P)}$ 20.1 Ar−C_{ipso}), 130.2 (s, Ar−C_{para}), 128.8 (s, Ar−C), 127.7 (s, Ar−C), 120.4 (d, $^1J_{(C,P)}$ 119.7 Hz, P*C*H=CHCH$_2$), 118.1 (d, $^1J_{(C,P)}$ 135.9 Hz, P*C*H=CHPh), 73.3 (d, $^2J_{(C,P)}$ 7.1 PO*C*H), 34.0 (d, $^3J_{(C,P)}$ 10.9 Hz, PCH=CH*C*H_2), 22.1 ppm (d, $^3J_{(C,P)}$ 7.1 Hz, POCH*C*H_3); ^{31}P NMR (101 MHz, $CDCl_3$) δ 24.8 ppm; IR (film) ν 1610 (C=C), 1209 (P=O); HRMS (CI) *m/z* calcd for $C_{13}H_{16}O_2P$ $[M + H]^+$ 235.0888, found 235.0890.

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Supporting Information Available: Detailed description of experimental procedures, NMR spectra, and X-ray crystal structures of *cis*-**6a**, *trans*-**6a**, and *trans*-**6f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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