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Substituent effects in the double diastereotopic differentiation of α-diazophosphonates via intramolecular cyclopropanation

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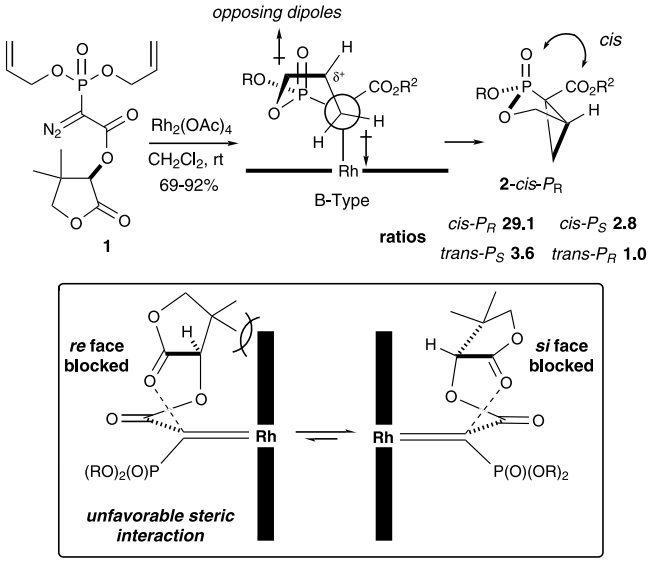
Abstract—The investigation of substituent effects in the double diastereotopic differentiation of substituted α-diazophosphonates using intramolecular cyclopropanation catalyzed by $Rh_2(OAc)_4$ is reported. Carbene facial selectivity in these transformations is dictated by substrate control in either of two ways: (i) exploitation of (*R*)-pantolactone as an auxiliary incorporated into the carboester functionality while probing olefinic substituent effects, or (ii) utilization of chiral, non-racemic allylic alcohols incorporated into the phosphonate moiety.

1. Introduction

The rich biological and synthetic profile of phosphorus-containing compounds[1] has prompted the development of new strategies for their synthesis. It is known that stereogenicity at or around a phosphorus center has profound effect on the biological and chemical properties.[2] Current synthetic efforts are therefore aimed at the development of asymmetric methods to access structurally diverse *P*-chiral phosphorus compounds that can have an assortment of medicinal, agricultural, and synthetic applications.[3] As part of our continuing program aimed at the synthesis of diverse *P*-chiral *P*-heterocycles,[4] we now report a study investigating substituent effects in the double diastereotopic differentiation of appropriately substituted α-diazophosphonoacetates employing intramolecular $Rh_2(OAc)_4$-catalyzed cyclopropanation.

Intramolecular cyclopropanation (ICP) mediated by $Rh_2(OAc)_4$ continues to provide a powerful tool for the construction of constrained systems from their diazo precursors, with high levels of diastereoselectivity and enantioselectivity having been achieved in numerous instances.[5] We recently reported a double diastereotopic differentiation strategy on an α-diazophosphonoacetate template **1** that utilized $Rh_2(OAc)_4$-catalyzed intramolecular cyclopropanation (ICP) employing the (*R*)-pantolactone auxiliary (Scheme 1).[4b] Selectivity in this system is dictated by chelation of the carbonyl moiety in the (*R*)-pantolactone to the metallo-carbenoid center effectively 'locking' the molecule in a rigid conformation and therefore blocking access to the *si* face of the reacting carbene (Davies model).[6] This method affords non-racemic, *P*-stereogenic [3.1.0]-bicyclic phosphonates **2** with good levels of olefin- (10.4:1) and diastereofacial-selectivity (6.9:1). The diastereomeric ratios in this study were conveniently determined using ^1H decoupled ^{31}P NMR analysis.



Scheme 1. Rationale for double diastereoselective ICP.

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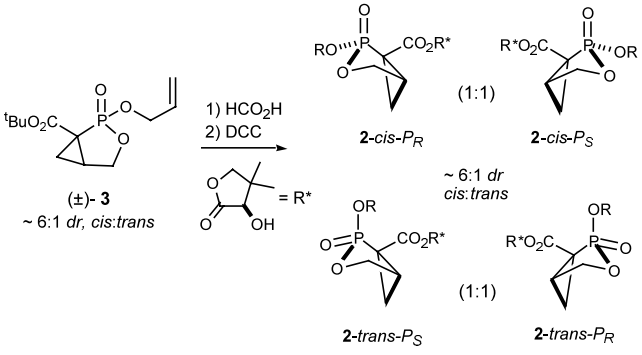
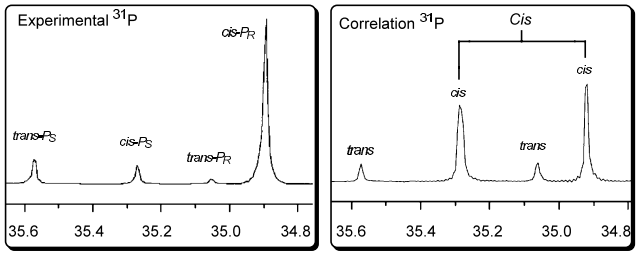
In order to associate each signal in the ^{1}H decoupled ^{31}P NMR spectra to its corresponding diastereomer, and to verify the group and facial selectivity, a correlation experiment was initially undertaken. Formic acid-mediated hydrolysis of *racemic* cyclopropanated, *tert*-butyl ester diastereomers (±)-**3** (~6:1, *cis:trans*),[7] followed by DCC coupling with (*R*)-pantolactone, produced the corresponding four diastereomers **2**-*cis*-P_R/**2**-*cis*-P_S and **2**-*trans*-P_R/**2**-*trans*-P_S, preserving the ~6:1 *cis:trans* ratio (Scheme 2). Subsequent ^{1}H decoupled ^{31}P NMR analysis of this sample and comparison to the experimental ^{31}P spectra allowed the assignment of each diastereomeric pair (*cis* versus *trans*) as denoted in Fig. 1. Furthermore, both *cis*-diastereomers were separated using silica gel chromatography and X-ray crystallographic analysis of each, **2**-*cis*-P_R and **2**-*cis*-P_S, provided full unambiguous assignment (Fig. 2). The production of **2**-*cis*-P_R as the major diastereomer is consistent with an *s*-*trans* orientation of the Rh=C and P=O π-systems (opposing-dipole) incorporating a B-type orientation of the reacting olefin and occurring from the *re*-face of the rhodium carbene (Scheme 1). Thus far, unambiguous assignment of each *trans*-diastereomer (**2**-*trans*-P_R versus **2**-*trans*-P_S) via X-ray crystallographic analysis has not been possible. Tentative assignment of the furthest downfield resonance as **2**-*trans*-P_S (Fig. 1) was made on the basis of analogy to the *cis*-diastereomeric series with the major *trans*-diastereomer also occurring from *re*-face attack on the rhodium carbenoid occurring from a B-type transition state.



Scheme 2. Synthesis of racemic cyclopropane diastereomers **2** for ^{31}P NMR correlation experiment.



Ratios

	2-*trans*-P_S	2-*cis*-P_S	2-*trans*-P_R	2-*cis*-P_R
Experimental	3.6	2.8	1.0	29.1
Correlation	1.0	6.0	1.0	6.0

Figure 1. Experimental and correlation ^{1}H decoupled ^{31}P spectra for the four cyclopropane diastereomers: **2**-*cis*-P_R/**2**-*cis*-P_S and **2**-*trans*-P_R/**2**-*trans*-P_S.

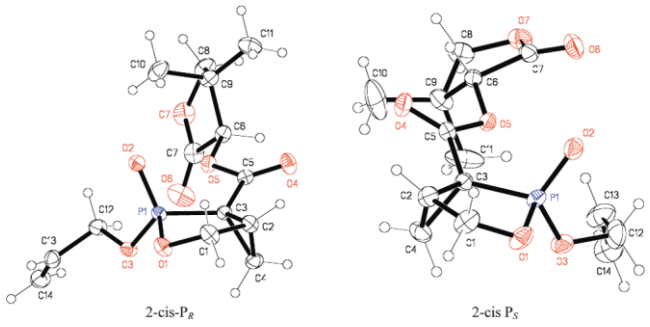
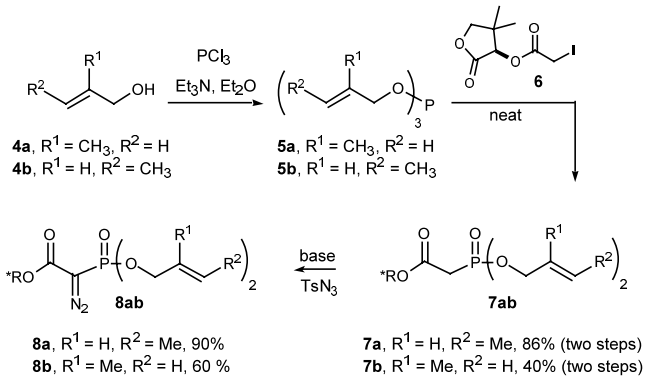


Figure 2. ORTEP representations of major and minor *cis*-diastereomers.

2. Results and discussion

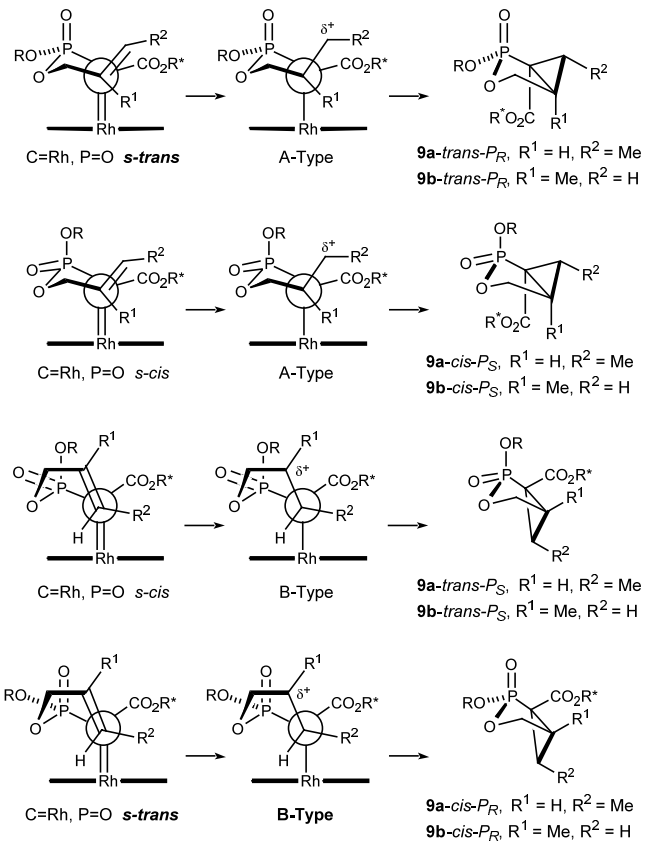
With these results in hand, we reasoned that investigation of the cyclopropanation of the corresponding bis-methallyl and bis-crotyl phosphonate esters, **7a** and **7b** (Scheme 3), respectively, would provide additional evidence for our previously proposed models vida infra. Thus, utilizing a similar protocol for the preparation of **1**, both **8a** and **8b** were synthesized as outlined in Scheme 3. Treatment of PCl_3 with Et_3N and either methallyl alcohol **4a** or *trans*-crotyl alcohol **4b** in diethyl ether generated the corresponding phosphites, trimethallyl phosphite **5a** and tricrotyl phosphite **5b** which were used directly without further purification. Subsequent Arbuzov reaction with (*R*)-pantolactone-iodoacetate produced the phosphonoacetates **7a** and **7b** in good to moderate yields over two steps. Final diazo transfer afforded the cyclopropanation precursors **8a** and **8b** in good yields.



Scheme 3.

Cyclopropanation of the α-diazophosphonoacetates **8a** and **8b** can proceed through one of eight possible transition states involving either of two A-type or B-

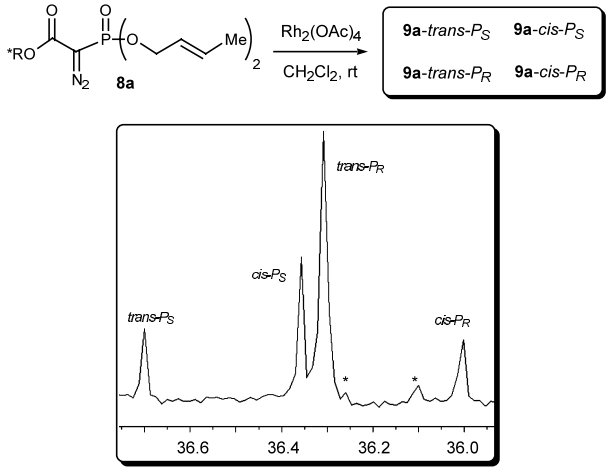
type transition states occurring from both the *re*- or *si*-face of the rhodium carbenoid. The ability of the (*R*)-pantolactone auxiliary to effectively block the *si*-face dictates *re*-face attack as the major pathway, leading to the four diastereomeric transition states as depicted in Scheme 4.



Scheme 4. Transition states leading to **9a** and **9b** occurring via *re*-face attack on the rhodium carbenoid.

A number of steric and electronic factors operate to govern the diastereofacial selectivity obtained from these four pathways, including: (i) the facial orientation between the reacting olefin and the rhodium carbene (A-type or B-type), which is dictated by charge stabilization,[8] (ii) the orientation of the Rh=C and P=O π-systems (*s-trans* or *s-cis*), in which 'opposing' dipole interactions between the P=O and the Rh-carbene moieties would favor the *s-trans* orientation, and (iii) steric interactions between the substituents R^1 and R^2 with the rhodium wall and/or the chiral auxiliary in the carboester functionality. In this complex analysis, a combination of effects is undoubtedly at play.

For the crotyl-phosphonate system **8a**, it can be seen that during the cyclopropanation, both A-type and B-type transition states lead to a build-up of positive charge on a secondary carbon. This contrasts with our previously explored allyl-based system **1**, which in theory progresses through B-type transition states since they alone generate positive charge build-up on a secondary carbon.[4b] We therefore presumed that cyclopropanation of the crotyl systems should display a significant amount of selectivity erosion. Indeed this was observed experimentally as shown in Fig. 3, thus giving additional proof to the previously described model.

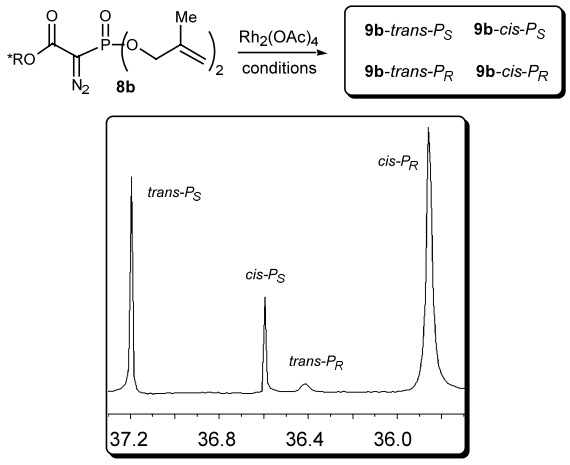


	Selectivity			
Conditions	**9a**-*trans*-P_S	**9a**-*cis*-P_S	**9a**-*trans*-P_R	**9a**-*cis*-P_R
CH_2Cl_2, rt	1.0	1.5	4.6	1.2

Figure 3. ^1H decoupled ^{31}P spectra for the $Rh_2(OAc)_4$-catalyzed ICP of α-diazophosphonoacetates **8a**. (*) ^{31}P resonances corresponding to trace cyclopropane diastereomers presumably derived from the *Z*-crotyl impurity in the starting material **7a**.

We have tentatively assigned the diastereomers as shown in Fig. 3 by correlation to the peak order of the ^{31}P NMR resonances of the allyl systems. Interestingly, the formation of the *trans*-P_R diastereomer as the major diastereomer in the ICP of the crotyl-based α-diazophosphonoacetate **8a** indicates the preference for an A-type transition state occurring from the *re*-face of the rhodium carbenoid with an opposing dipole orientation of the Rh=C and P=O π-systems (*s-trans*). Mechanistically, this implies that this opposing dipole orientation plays a significant role in dictating the stereochemical course of these ICP reactions. Furthermore, additional steric factors may be operative, whereby there are unfavorable interactions between the terminal methyl group of the crotyl-based rhodium carbenoid species generated from **8a** ($R^1 = H$, $R^2 = Me$) and the rhodium wall in B-type transition states (Scheme 4).

We next focused on the cyclopropanation of the methallyl-based α-diazophosphonoacetate **8b**. In accordance to the proposed transition states (Scheme 4), this system should generate a heavily favored B-type transition state in which positive charge build-up occurs at a tertiary carbon. Experimentally it was found that the selectivity in the *cis*-series slightly decreased (8.7:1), when compared to the original allyl case (10.4:1.0) while the *trans* selectivity increased slightly to 6.1:1.0 from 3.6:1.0 (Fig. 4). It is worth noting that the rate of



	Selectivity			
Conditions	**9**-*trans*-P_S	**9**-*cis*-P_S	**9**-*trans*-P_R	**9**-*cis*-P_R
CH_2Cl_2, rt	**6.1**	**2.3**	**1.0**	**20.1**
Et_2O, reflux	3.2	3.0	1.0	18.3
CH_2Cl_2, reflux	4.2	2.9	1.0	12.2
PhH, reflux	2.8	2.4	1.0	8.7

Figure 4. ^1H decoupled ^{31}P spectra for the $Rh_2(OAc)_4$-catalyzed ICP of α-diazophosphonoacetates **8b**.

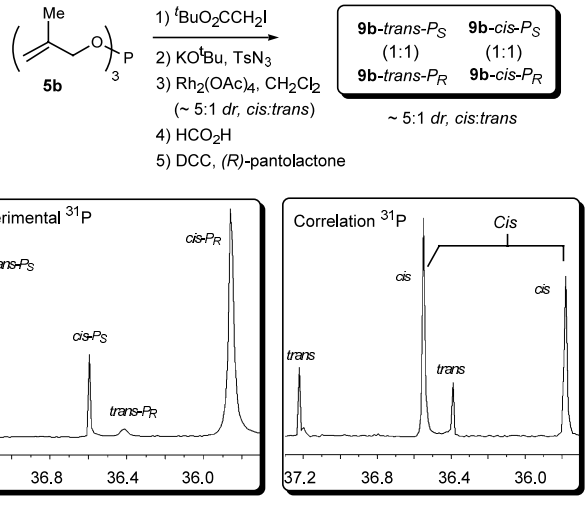
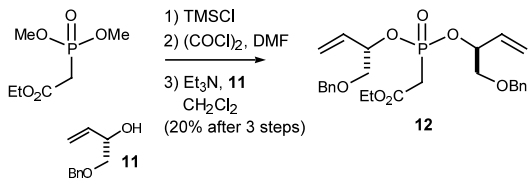


Figure 5. Experimental and correlation ^1H decoupled ^{31}P spectra for the four cyclopropane diastereomers: **9b**-*cis*-P_R/**9b**-*cis*-P_S and **9b**-*trans*-P_R/**9b**-*trans*-P_S.

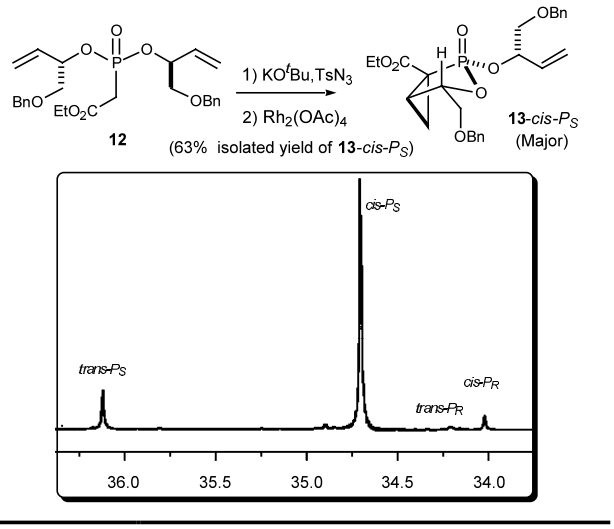
reaction of **8b** was considerably faster in comparison to its allylic counterpart **1** (1–2 h versus 3–4 h reaction time). This is in agreement with a more favorable positive charge build-up on a tertiary carbon in the methallyl case as compared to the build-up of positive charge on a secondary carbon in the allylic case. The fact that we do not see a large increase in selectivity in the ICP of **8b** would support the notion that the minor diastereomers, *cis*-P_S and the *trans*-P_R, do not arise from A-type transition states, but instead are generated via *si*-face attack on the rhodium carbenoid undergoing B-type transitions.[4b] The A-type transition states are further disfavored due to steric interactions between the internal methyl group of the rhodium carbenoid species generated from **8b** (R^1 = Me, R^2 = H) and the rhodium wall (Scheme 4).

Correlation experiments for **9b** again provided further proof for the ^{31}P assignments (Fig. 5). An analogous synthesis of the corresponding racemic mixture of the four diastereomers **9b**-*cis*-P_R/**9b**-*cis*-P_S and **9b**-*trans*-P_R/**9b**-*trans*-P_S, began with an Arbuzov reaction between trimethallylphosphite **5b** and *tert*-butyliodoacetate (Fig. 5). Subsequent diazo transfer with KO^{t}Bu and TsN_3 followed by treatment with $Rh_2(OAc)_4$ produced the diastereomeric pair of cyclopropanes as a ~5:1 mixture of *cis*- and *trans*-diastereomers. Formic acid-mediated hydrolysis followed by DCC coupling with the (*R*)-pantolactone moiety, produced the corresponding four diastereomers **9b**-*cis*-P_R/**9b**-*cis*-P_S and **9b**-*trans*-P_R/**9b**-*trans*-P_S, preserving the ~5:1 *cis:trans* ratio. The corresponding chemical shifts seen in Fig. 5 parallel those attained in the correlation experiments for the four cyclopropane diastereomers **2** derived from the α-diazophosphonoacetate **1** presented in Fig. 1.

The final example we investigated involved the desymmetrization of a novel pseudo-C_2-symmetric template **12** (Scheme 5) possessing a nonstereogenic, prochiral phosphorus atom bearing two diastereotopic olefins, with each olefin possessing two diastereotopic faces. We had previously shown that ring-closing metathesis (RCM) was an effective tool in the diastereotopic differentiation of pseudo-C_2-symmetric phosphonamides.[4a] We felt that a similar desymmetrization strategy employing the pseudo-C_2-symmetric phosphonoacetate **12** would provide access to the novel *P*-chiral [3.1.0]-bicyclic system **13** (Fig. 6). In our previously reported desymmetrization utilizing RCM,[4a] olefin substitution was utilized to direct the initial metathesis event, a prerequisite for desymmetrization strategies involving pseudo-C_2-symmetric templates.[4a,9] With the phosphonoacetate **12**, this is not an issue, since diazotization guarantees regiospecific carbene formation α- to the phosphonyl group. We therefore believed that the equatorial preference of the substituent contained in the allylic appendage would dictate *si*-facial attack on the rhodium carbene from a B-type transition state employing the *s-trans* orientation of the Rh=C and P=O π-systems (opposing dipole), producing the *cis*-P_S diastereomer, **13**-*cis*-P_S, as the major diastereomer.



Scheme 5. Preparation of pseudo-C_2-symmetric phosphonoacetate **12**.



Selectivity

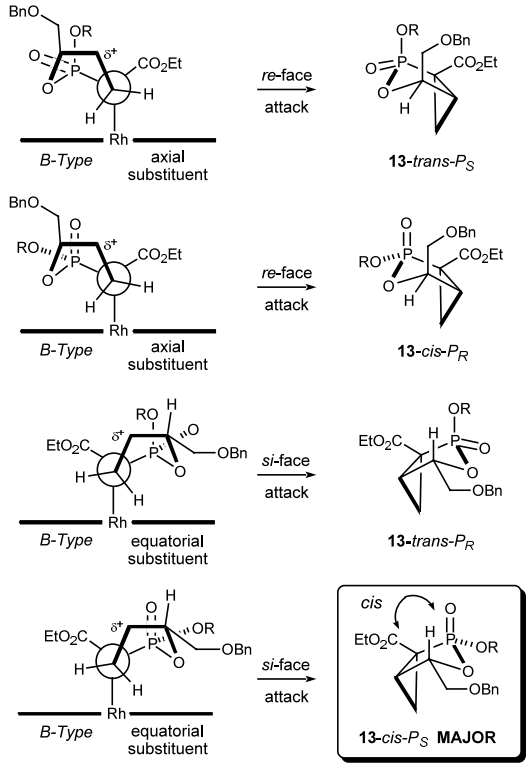
Conditions	13-*trans*-P_S	13-*cis*-P_S	13-*trans*-P_R	13-*cis*-P_R
CH_2Cl_2, RT	7.4	44.8	1.0	2.4
CH_2Cl_2, reflux	5.8	29.2	1.0	1.9

Figure 6. ^{1}H decoupled ^{31}P spectra for the $Rh_2(OAc)_4$-catalyzed ICP of the corresponding α-diazophosphonoacetates of **12**.

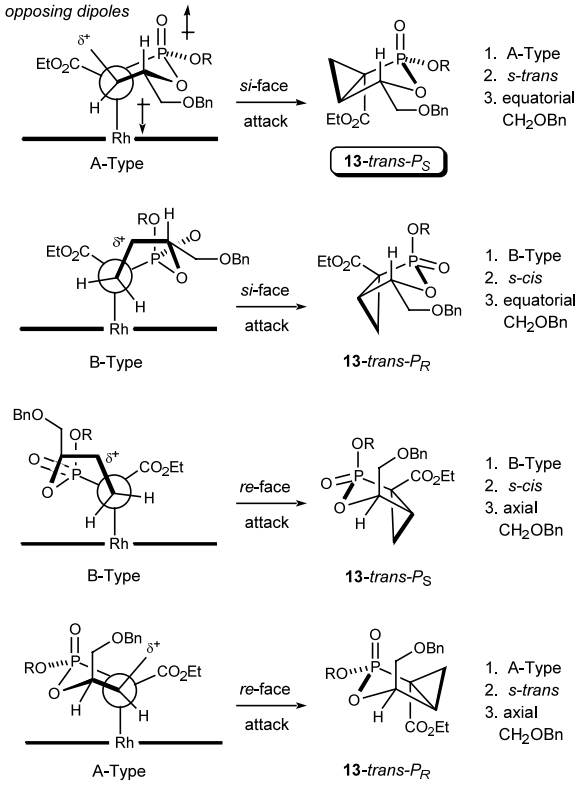
The synthesis of the requisite phosphonoacetate **12** began with TMSCl-mediated deprotection of dimethylethyl phosphonoacetate (Scheme 5). Acid chloride formation, followed by condensation of the readily prepared chiral, non-racemic allylic alcohol **11**[10] affords **12** in modest yield (unoptimized, 20% over three steps).

Diazotization and subsequent cyclopropanation, catalyzed by $Rh_2(OAc)_4$, generated the four diastereomeric [3.1.0]-bicycles **13** with excellent group (olefin) selectivity (18.7:1) and good diastereofacial (*cis*/*trans*) selectivity (5.6:1). The major diastereomer arising from ICP of the corresponding α-diazophosphonoacetate of **12** has been tentatively assigned as the *cis*-P_S diastereomer, **13**-*cis*-P_S. We have based this assignment on correlation of the ^{31}P NMR spectra with the allyl system **1** which is consistent with the rationale noted above (Scheme 6). In addition, chromatography elution order is consistent with the *cis*-P_S assignment,[11] and ^{1}H NMR chemical shift trends support the *cis*-assignment.[12]

Correlation of the ^{31}P spectra with the allyl system **1**, tentatively leads us to assign the major *trans*-diastereomer as **13**-*trans*-P_S. The *trans*-assignment was further supported by ^{1}H NMR chemical shift data.[12] As shown in Scheme 7, this product can arise from either an A-type transition state occurring with the favorable *s*-*trans* orientation of the Rh=C and P=O π-systems (opposing dipole), and with equatorial placement of the benzyl ether substituent, or via a B-type transition state occurring with the unfavorable *s*-*cis* orientation of the Rh=C and P=O π-systems, and with axial placement of the benzyl ether substituent. This result is contrary to the expected type-B transition state model portrayed in Schemes 6 and 7 that predicts **13**-*trans*-P_R as the major diastereomer (B-type, *s*-*cis*, and equatorial benzyl ether). With all factors



Scheme 6. Transition states leading to phosphonate **13** occurring via B-type transition states.



Scheme 7. Transition states leading to the *trans* diastereomers, **13**-*trans*-P_R and **13**-*trans*-P_S.

considered, we believe that the *s-trans* orientation of the Rh=C and P=O π-systems may be the most influential factor in determining facial preferences in ICP, since in this pivotal example, it overrides the predicted preference for a B-type transition state.[13]

3. Conclusions

We have demonstrated that substituents play an important role in the double diastereotopic differentiation strategy of α-diazophosphonoacetate templates utilizing $Rh_2(OAc)_4$-catalyzed ICP employing the (*R*)-pantolactone auxiliary. Furthermore, we have reported a double diastereoselective ICP of the pseudo-C_2-symmetric phosphonate **12** that occurs with excellent selectivity. This study represents part of our continuing program aimed at the synthesis of diverse *P*-heterocycles. Additional efforts in this area are underway and will be reported in due course.

4. Experimental

4.1. Representative diazotization procedure

A solution of the phosphonoacetate and CH_2Cl_2 was cooled to 0°C. Base (KO^{t}Bu or Et_3N) was added, the reaction stirred for 5 min, and TsN_3 was added. The reaction was brought to room temperature and monitored by TLC. Once complete, the crude reaction was dissolved in EtOAc, washed with H_2O (2×), brine (2×), and dried ($MgSO_4$). The organic portion was concentrated under reduced pressure. Flash chromatography afforded purified α-diazophosphonoacetates.

4.2. Representative cyclopropanation procedure

A solution of the α-diazophosphonoacetate in CH_2Cl_2 (0.05 M) was charged with $Rh_2(OAc)_4$ (0.05 equiv.) under an atmosphere of argon. Once the reaction was complete, the reaction was directly analyzed by ^1H decoupled ^{31}P spectroscopy to elucidate stereoselectivity.

4.3. [Bis-(2-methylallyloxy)-phosphoryl]-acetic acid *tert*-butyl ester

Trimethallylphosphite was generated as described before for **7b** using methallyl alcohol (3.00 g, 41.6 mmol), Et_3N (4.55 g, 45.0 mmol) and PCl_3 (1.88 g, 13.64 mmol). The crude phosphite was added dropwise to a neat solution of ^{t}butyliodoacetate (8.25 g, 34.1 mmol) at 90°C. Once complete (GC analysis), the reaction was directly subjected to flash chromatography (2:1 hexanes/EtOAc) to afford 2.4 g (57.8%, two steps) of pure phosphonoacetate as a clear oil. FTIR 1730, 1661, 1286, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 2H, broad), 4.85 (s, 2H, broad), 4.41 (d, $J_{HP}=7.7$ Hz, 4H), 2.85 (d, $J_{HP}=21.6$ Hz, 2H), 1.68 (s, 6H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.32 (d, $J_{CP}=6.3$ Hz), 139.83 (d, $J_{CP}=6.6$ Hz), 112.89, 81.78, 69.12 (d, $J_{CP}=6.0$ Hz), 35.37 (d, $J_{CP}=134.4$ Hz), 27.59, 18.70; ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.10; HRMS calcd for $C_{14}H_{26}O_5P$ (M+H$^+$) required 305.1518, found 305.1506.

4.4. [Bis-(2-methyl-allyloxy)-phosphoryl]-diazo-acetic acid *tert*-butyl ester

tert-Butyldimethallylphosphonoacetate (425 mg, 1.40 mmol) in 4 mL CH_2Cl_2 was subjected to the general diazotization protocol using KO^{t}Bu (276 mg, 2.46 mmol) and TsN_3 (485 mg, 2.46 mmol). Flash chromatography (2:1 hexanes/EtOAc) produced 355 mg (77%) of pure α-diazophosphonoacetate as a clear yellow oil. FTIR 2128, 1698, 1295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (s, 2H, broad), 4.91 (s, 2H, broad), 4.47 (dd, $J_{HP}=8.4$, $J=3.8$ Hz, 4H), 1.74 (s, 6H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.77 (d, $J_{CP}=7.1$ Hz), 113.62, 83.05, 70.44 (d, $J_{CP}=5.5$ Hz), 28.14, 18.97; ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.49; HRMS calcd for $C_{14}H_{24}N_2O_5P$ (M+H$^+$) required 331.1423, found 331.1416.

4.5. [Bis-((*E*)-but-2-enyloxy)-phosphoryl]-acetic acid (3*R*)-4,4-dimethyl-2-*oxo*-tetrahydrofuran-3-yl ester, 7a

Tricrotylphosphite was generated as described for trimethallylphosphite using crotyl alcohol (2.05 mL, 24.0 mmol), Et_3N (3.35 mL, 24.0 mmol) and PCl_3 (1.0 g, 7.3 mmol). The crude phosphite was subsequently added dropwise to a heated (90°C) neat solution of pantolactone-iodoacetate (6.6 g, 21.8 mmol). Once complete (GC analysis), the crude reaction was directly subjected to flash chromatography (2:1 hexanes/EtOAc) to generate 1.9 g (86%, two steps) of pure phosphonoacete **7a** as a clear oil. $[\alpha]_D^{25}=-2.2$ (*c* 2.0, $CHCl_3$); FTIR 1799, 1748, 1674, 1268 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.80–5.73 (m, 2H), 5.59–5.53 (m, 2H), 5.34 (s, 1H), 4.51–4.44 (m, 4H), 4.00 (d, $J=9.0$ Hz, 1H), 3.97 (d, $J=9.0$ Hz, 1H), 3.07 (dd, $J=55.0$, $J_{HP}=14.3$ Hz, 1H), 3.02 (dd, $J=54.8$, $J_{HP}=14.3$ Hz, 1H), 1.67 (s, 3H), 1.66 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.70, 164.62 (d, $J_{CP}=6.4$ Hz), 131.78, 131.76, 125.42 (d, $J_{CP}=6.4$ Hz), 125.37 (d, $J_{CP}=6.2$ Hz), 76.00, 75.67, 67.14 (d, $J_{CP}=6.2$ Hz), 67.05 (d, $J_{CP}=6.2$ Hz), 40.32, 34.24 (d, $J_{CP}=133.0$ Hz), 22.60, 19.52, 17.50; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.13; HRMS calcd for $C_{16}H_{26}O_7P$ (M+H$^+$) required 361.1416, found 361.1415.

4.6. [Bis-((*E*)-but-2-enyloxy)-phosphoryl]-diazo-acetic acid (3*R*)-4,4-dimethyl-2-*oxo*-tetrahydrofuran-3-yl ester, 8a

Phosphonoacetate **7a** (45 mg, 0.15 mmol) in 0.3 mL CH_2Cl_2 was subjected to the general diazotization protocol using Et_3N (0.041 mL, 0.27 mmol) and TsN_3 (44 mg, 0.22 mmol). Flash chromatography (2:1 hexanes/EtOAc) produced 43 mg (90%) of pure α-diazophosphonoacetate **8a** as a clear yellow oil. $[\alpha]_D^{25}=+4.0$ (*c* 0.50, $CHCl_3$); FTIR 2136, 1789, 1712, 1280 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.89–5.81 (m, 2H), 5.68–5.58 (m, 2H), 5.40 (s, 1H), 4.61–4.51 (m, 4H), 4.07 (d, $J=9.0$ Hz, 1H), 4.03 (d, $J=9.0$ Hz, 1H), 1.74 (s, 3H), 1.72 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.58, 132.47, 132.42, 125.16, 125.10, 76.09, 75.82, 68.31 (d, $J_{CP}=5.6$ Hz), 68.13 (d, $J_{CP}=5.4$ Hz), 40.14, 22.82, 19.74, 17.72, 17.71; ^{31}P NMR (162 MHz, $CDCl_3$) δ 10.25; HRMS calcd for $C_{16}H_{24}N_2O_7P$ (M+H$^+$) required 387.1321, found 387.1320.

4.7. [Bis-(2-methyl-allyloxy)-phosphoryl]-acetic acid (3*R*)-4,4-dimethyl-2-*oxo*-tetrahydrofuran-3-yl ester, 7b

Step a: in a 50 mL round-bottom flask equipped with an exit needle fitted with a drierite-filled syringe, a solution of Et_3N (2.12 mL, 15.2 mmol) and methallyl alcohol (1.00 g, 13.9 mmol) in 15 mL dry Et_2O was cooled to 0°C under an atmosphere of argon. PCl_3 (636 mg, 4.6 mmol) was added dropwise. Once addition was complete, the reaction was allowed to stir at ambient temperature for 1 h. The salts were filtered and washed with dry Et_2O. The resulting organic filtrate was concentrated under reduced pressure generating crude trimethallylphosphite, which was used directly in the subsequent Arbuzov reaction. Step b: neat pantolactone-iodoacetate (4.13 g, 13.9 mmol) was heated to 90°C in a 10 mL round-bottom flask and subsequently charged with dropwise addition of trimethallylphosphite. Once complete (GC analysis), the reaction was directly subjected to flash chromatography (3:1 then 2:1 hexanes/EtOAc) producing 670 mg (40%, two steps) of pure phosphonoacete **7b** as a clear oil. $[\alpha]_D^{25} = -0.5$ (*c* 0.95, $CHCl_3$); FTIR 1798, 1748, 1660, 1270 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 5.04 (s, 2H, broad), 4.94 (s, 2H, broad), 4.55–4.44 (m, 4H), 4.04 (d, $J = 9.0$ Hz, 1H), 4.00 (d, $J = 9.0$ Hz, 1H), 3.18 (dd, $J = 36.4$, $J_{HP} = 14.4$ Hz, 1H), 3.13 (dd, $J = 38.3$, $J_{HP} = 16.6$ Hz, 1H), 1.76 (s, 6H), 1.19 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 164.64 (d, $J_{CP} = 6.3$ Hz), 139.83 (d, $J_{CP} = 6.1$ Hz), 139.77 (d, $J_{CP} = 6.2$ Hz), 113.68, 113.66, 76.14, 75.92, 69.89 (d, $J_{CP} = 6.3$ Hz), 69.76 (d, $J_{CP} = 6.2$ Hz), 40.40, 34.02 (d, $J_{CP} = 134.9$ Hz), 22.80, 19.69, 18.95, 18.93; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.17; HRMS calcd for $C_{16}H_{26}O_7P$ ($M+H^+$) required 361.1416, found 361.1401.

4.8. [Bis-(2-methyl-allyloxy)-phosphoryl]-diazo-acetic acid (3*R*)-4,4-dimethyl-2-*oxo*-tetrahydrofuran-3-yl ester, 8b

Phosphonoacetate **7b** (349 mg, 0.97 mmol) in 2.5 mL CH_2Cl_2 was subjected to the general diazotization protocol using KO^{t}Bu (163 mg, 1.45 mmol) and TsN_3 (286 mg, 1.45 mmol). Flash chromatography (2:1 hexanes/EtOAc) produced 243 mg (65%) of pure α-diazophosphonoacetate **8b** as a clear oil. $[\alpha]_D^{25} = +1.3$ (*c* 0.30, $CHCl_3$); FTIR 2138, 1789, 1713, 1282 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (s, 1H), 5.08 (s, 2H, broad), 4.97 (d, $J = 5.8$ Hz, 2H), 4.59–4.51 (m, 4H), 4.06 (d, $J = 9.0$ Hz, 1H), 4.03 (d, $J = 9.5$ Hz, 1H), 1.79 (s, 3H), 1.78 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.55, 139.61 (d, $J_{CP} = 6.9$ Hz), 139.57 (d, $J_{CP} = 6.9$ Hz), 114.18, 114.07, 75.91, 75.74, 70.85 (d, $J_{CP} = 5.6$ Hz), 70.77 (d, $J_{CP} = 5.5$ Hz), 39.88, 22.83, 19.75, 19.02, 19.00; ^{31}P NMR (162 MHz, $CDCl_3$) δ 10.45; HRMS calcd for $C_{16}H_{24}N_2O_7P$ ($M+H^+$) required 387.1321, found 387.1325.

4.9. [Bis-((1*S*)-1-benzyloxymethyl-allyloxy)-phosphoryl]-acetic acid ethyl ester, 12

In an argon-flushed, screw-cap pressure tube, dimethylethylphosphonoacetate (210 mg, 1.1 mmol) was taken up in neat TMSCl (0.68 mL, 5.4 mmol) and stirred at 100°C for 72 h. The mixture was concentrated under reduced pressure. In a 25 mL round-bottom flask purged with argon and equipped with a drierite-filled syringe, the resulting bis-TMS-phosphonic acid was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Oxalyl chloride (0.19 mL, 2.2 mmol) was added followed by a single drop of DMF (which induced gas extrusion). Once complete (ceasing of gas extrusion), the crude reaction was concentrated under reduced pressure. The crude phosphonyl dichloridate was rediluted with CH_2Cl_2 (5 mL), cooled to 0°C, and both Et_3N (0.45 mL, 3.2 mmol) and allylic alcohol **11** were added. Once addition was complete, the reaction was refluxed under argon for 1 h. The crude reaction was diluted with EtOAc, washed with H_2O (2×), brine (2×), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (1:1 hexanes/EtOAc) produced pure **12** as a colorless oil (100 mg 19%, three steps). $[\alpha]_D^{25} = -1.8$ (*c* 0.40, $CHCl_3$); FTIR 1736, 1267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 10H), 5.85 (dddd, $J = 40.8$, 17.0, 10.6, 6.3 Hz, 2H), 5.41 (dd, $J = 26.0$, 17.2 Hz, 2H), 5.24 (dd, $J = 38.2$, 10.6 Hz, 2H), 5.21–5.15 (m, 1H), 5.14–5.06 (m, 1H), 4.57 (dd, $J = 11.9$, 6.1 Hz, 2H), 4.52 (d, $J = 11.9$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.62–3.52 (m, 4H), 3.06 (dd, $J = 18.8$, 14.5 Hz, 1H), 3.02 (dd, $J = 18.8$, 14.6 Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.67 (d, $J_{CP} = 6.9$ Hz), 137.83 (d, $J_{CP} = 6.7$ Hz), 133.81 (d, $J_{CP} = 4.0$ Hz), 133.73 (d, $J_{CP} = 4.3$ Hz), 128.37, 128.34, 127.75, 127.67, 118.54, 118.27, 73.17, 73.14, 72.42 (d, $J_{CP} = 5.2$ Hz), 72.35 (d, $J_{CP} = 5.2$ Hz), 61.39, 35.42 (d, $J_{CP} = 137.7$ Hz), 14.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.77; HRMS calcd for $C_{26}H_{34}O_7P$ ($M+H^+$) required 489.2042, found 489.2050.

4.10. (4*S*)-4-Benzyloxymethyl-2-((1*S*)-1-benzyloxymethyl-allyloxy)-2-oxo-3-oxa-2λ^5-phospha-bicyclo-[3.1.0]hexane-1-carboxylic acid ethyl ester, 13-*cis*-P_S (major)

Diazotization of phosphonoacetate **12** was carried out using the general diazotization protocol in 62% yield. The resulting α-diazophosphonoacetate (20 mg, 0.04 mmol) was dissolved in 1.1 mL CH_2Cl_2 and subjected to the general cyclopropanation protocol using 1 mg $Rh_2(OAc)_4$. The reaction was stirred at room temperature until complete (TLC analysis, 72 h). The crude mixture was concentrated under reduced pressure and directly subjected to flash chromatography (2:1 hexanes/EtOAc) to yield 12 mg (63%) of the single diastereomer **13**-*cis*-P_S as a clear oil.

13-*cis*-P_S (major): $[\alpha]_D^{25} = +4.6$ (*c* 1.00, $CHCl_3$); FTIR 1727, 1279 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H), 5.94 (ddd, $J = 16.8$, 10.7, 6.0 Hz, 1H), 5.45 (dd, $J = 17.2$, 1.2 Hz, 1H), 5.30–5.25 (m, 1H), 5.29 (dd, $J = 10.6$, 1.2 Hz, 1H), 4.64–4.56 (m, 3H), 4.34 (ddd, $J = 19.4$, 7.2, 5.7 Hz, 1H), 4.27–4.15 (m, 2H), 3.82 (dd, $J = 9.9$, 5.6 Hz, 1H), 3.73 (dd, $J = 9.9$, 7.2 Hz, 1H), 3.67–3.57 (m, 3H), 2.67 (ddd, $J = 8.1$, 8.1, 5.9 Hz, 1H), 1.69 (ddd, $J = 10.1$, 8.4, 4.8 Hz, 1H), 1.50–1.44 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.96 (d, $J_{CP} = 10.1$ Hz), 137.87, 137.60, 133.64 (d, $J_{CP} = 4.8$ Hz), 128.44, 128.31, 127.83, 127.70, 127.61,

118.23, 75.34 (d, $J_{CP}=4.6$ Hz), 73.69, 73.10, 72.09 (d, $J_{CP}=3.9$ Hz), 71.54, 62.02, 29.84 (d, $J_{CP}=8.3$ Hz), 29.69, 22.35 (d, $J_{CP}=176.5$ Hz), 18.49 (d, $J_{CP}=2.6$ Hz), 14.04; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.71; HRMS calcd for $C_{26}H_{32}O_7P$ ($M+H^+$) required 487.1886, found 487.1871.

13-*trans*-P_S (minor): $[\alpha]_D^{25}=+8.2$ (*c* 0.50, $CHCl_3$); FTIR 1725, 1273 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 10H), 5.96 (ddd, $J=17.1$, 10.6, 6.5 Hz, 1H), 5.45 (d, $J=17.2$ Hz, 1H), 5.29 (d, $J=10.6$ Hz, 1H), 5.24–5.19 (m, 1H), 4.61–4.48 (m, 3H), 4.35 (ddd, $J=19.9$, 6.6, 6.6 Hz, 1H), 4.16–4.10 (m, 1H), 4.08–4.02 (m, 1H), 3.76–3.55 (m, 5H), 2.59–2.53 (m, 1H), 1.72 (ddd, $J=11.0$, 8.4, 5.2 Hz, 1H), 1.62–1.56 (m, 1H), 1.21 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.87 (d, $J_{CP}=8.8$ Hz), 137.93, 137.52, 134.52, 128.45, 128.37, 127.87, 127.66, 127.59, 118.68, 77.69 (d, $J_{CP}=6.7$ Hz), 73.52, 73.25, 71.99 (d, $J_{CP}=8.4$ Hz), 61.99, 29.07, 29.02, 22.11 (d, $J_{CP}=179.8$ Hz), 17.71, 14.00; ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.19.

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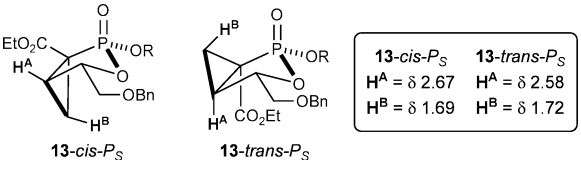
10. **11** was prepared from addition of trimethylsulfonium ylide to (*S*)-benzyl-glycidyl ether, see: Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255–1259.
11. After chromatographic separation, we found that the relative position of the major diastereomer **13** in the elution order of all four diastereomers was identical to the position of **2-*cis*-P_S**, therefore supporting the assignment of this major diastereomer as **13-*cis*-P_S**.
12. The ^{1}H chemical shift of the protons on the bicyclic system which are *endo* to the P=O group are further downfield than their *exo* counterparts.



13. It is worth noting that the olefin selectivity within the *trans*-diastereomers of **13** (**13**-*trans*-P_S versus **13**-*trans*-P_R) also substantially increased to a ratio of 7.4:1 (from 3.6:1 for the allyl-based system **1**).