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Allylic hydroxy phosphonates: versatile chiral building blocks

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Abstract

Allylic hydroxy phosphonates are converted into β and γ substituted amino phosphonates using a series of palladium-catalyzed reactions. The judicious selection of nitrogen nucleophile and palladium catalyst allow for excellent regio- and stereochemical control. Palladium(0)-catalyzed amine addition or tosyl carbamate rearrangement gives rise to the γ-substituted phosphonates, whereas, reaction of tosyl carbamates with palladium (II) and base gives oxazolidinones (β-substitution).

Keyword: Hydroy phosphonate

1. Introduction

Recent advances in catalytic asymmetric phosphonylation of unsaturated aldehydes [1] and other methods [2–4] have resulted in readily accessible allylic hydroxy phosphonates in good to excellent enantiomeric excess. As part of a continued effort to explore the application of hydroxy phosphonates as building blocks for the synthesis of structurally more complex, and biologically interesting molecules [5], we wanted to identify a series of stereoselective (or stereospecific) transformations. Of particular interest were methods for the introduction of nitrogen substituents to the β and γ positions of the phosphonate alkyl chain, since these are present in several examples of biologically active phosphonates and phosphonic acids [6,7].

It has been recognized that allylic hydroxy phosphonates display some of the rich chemistry associated with allylic alcohols, however, the steric and electronic influence of the phosphorus moiety can enhance the stereochemical and regiochemical outcome of the reactions. The effect of the phosphonate moiety is observed in the palladium-catalyzed addition of nucleophiles to the corresponding acetate and carbonate derivatives of allylic hydroxy phosphonates [8,9,5]. Zhu and Lu [8] reported that amine and malonate nucleophiles added to α-acetoxy allylic phosphonates to give exclusively the γ-substituted vinyl phosphonates **4** in high yield. Palladium-catalyzed addition of nitrogen and carbon nucleophiles to racemic allylic phosphonates were later employed by others in the successful synthesis of fosmidomycin analogs and ω-phosphono amino acids [9]. We first communicated that amines added to the carbonate derivatives of non-racemic allylic hydroxy phosphonate with complete chirality transfer [5a]. More recently, we applied the palladium(0)-catalyzed intermolecular addition of carbon nucleophiles to the asymmetric synthesis of the natural products turmerone and enterolactone [5b,c]. Less well explored are Pd(II) pathways for the structural elaboration of allylic hydroxy phosphonates [5a]. Herein, we report in full the our studies of both palladium (0) and palladium(II)-catalyzed pathways for the addition of nitrogen nucleophiles to non-racemic allylic hydroxy phosphonate derivatives.

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2. Results and discussion

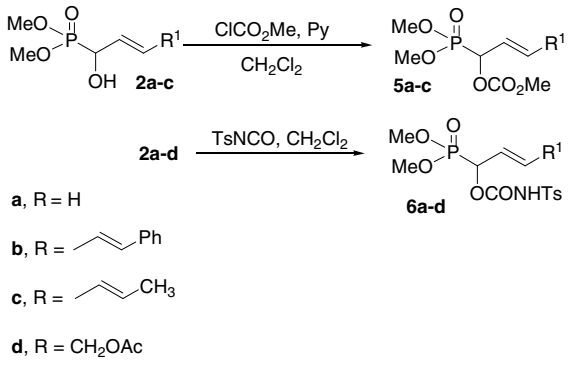
2.1. Preparation of allylic hydroxy phosphonates

Hydroxy phosphonates **2a**–**c** were prepared by the addition of dimethylphosphite to the corresponding aldehydes **1a**–**c** (Scheme 1). The non-racemic phosphonates were prepared by catalytic asymmetric phosphonylation using dimethyl tartrate and $Ti(OiPr)_4$ as catalyst [1a], whereas the racemic compounds were prepared using Et_3N [10] or $Ti(OiPr)_4$. The enantiomeric excess of the non-racemic phosphonates was determined by HPLC on a chiral stationary phase [1a,11a] or ^{31}P NMR spectroscopy with quinine as the shift reagent [11b].

Hydroxy phosphonate **2d**, which contains additional functionality at the δ position, was formed by the phosphonylation of *trans*-4-acetoxy-2-buten-1-al **1d**. The *trans* aldehyde **1d** was prepared in modest yield (55%) from commercially available *cis*-but-2-ene-1,4-diol **3** by acetylation with polyvinylpyridine (PVP) and AcCl in acetonitirile, and oxidation of the resulting alcohol **4** with PCC in CH_2Cl_2. The aldehyde **1d** was phosphonylated to provide both *racemic* and non-*racemic* allylic hydroxy phosphonate **2d**.

The hydroxy phosphonates **2** were treated with methyl chloroformate in pyridine to give the corresponding carbonates **5a**–**c**, or with tosyl isocyanate to give the tosyl carbamates **6a**–**d** (Scheme 2). The methyl carbonates were oils, whereas the tosyl carbmates were generally colorless crystalline solids.

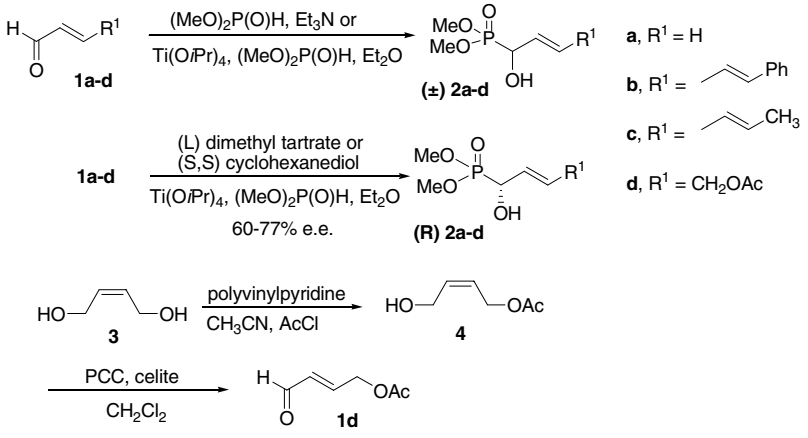
An alternative approach for the preparation of allylic phosphonates involved the cross-metathesis reaction of acrolein derived phosphonate **5a** with terminal alkenes in the presence of Grubbs second generation ruthenium benzylidene catalyst (Scheme 3) [5b,12]. The required alkenes **10a** and **10b** were prepared by reductive amination of the aldehydes **8a** and **8b**, respectively, with glycine methyl ester followed by protection of the secondary amine by treatment with Boc anhydride. Cross-metathesis of the alkenes **10a** and **10b** with 2 equivalents of phosphonate **5a** in toluene proceeded smoothly. The crude products were deprotected with TFA to provide the amines **5e** and **5f** in good overall yields.



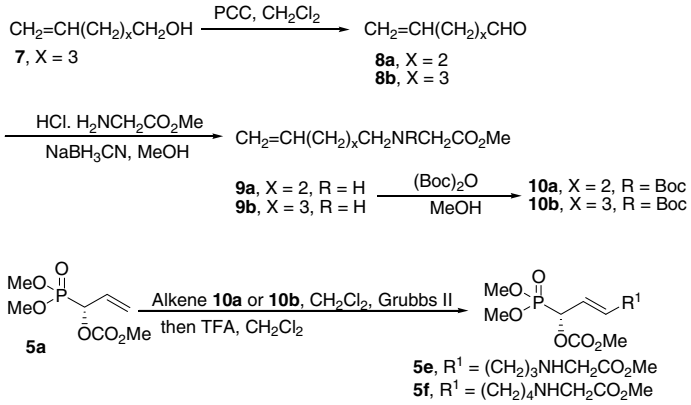
Scheme 2.

2.2. Palladium(0)-catalyzed addition of amine nucleophiles

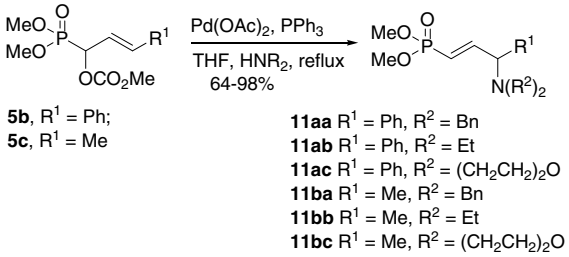
Zhu and Lu [8] had shown that α-acetoxy allylic phosphonates undergo palladium-catalyzed addition of amine nucleophiles to give γ-substituted vinyl phosphonates in high yield. The nucleophile adds exclusively to the γ-position, with migration of the double bond into "conjugation" with the phosphoryl group. In most cases, addition of amines resulted in the formation of the *E* vinyl phosphonate (>10:1). In our hands, these reactions were slow and did not work well for a wider range of amines or phosphonates. However, the carbonate derivatives of allylic hydroxy phosphonates **5** underwent palladium-catalyzed amination more rapidly than the corresponding acetates to give amines **11** in high yield (Scheme 4). The range of amine nucleophiles and



Scheme 1.



Scheme 3.



Scheme 4.

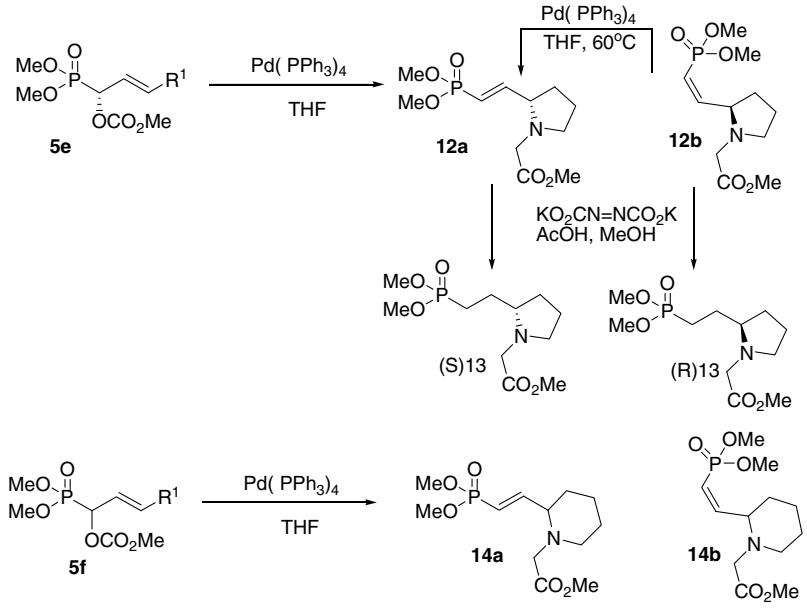
phosphonates compatible with the reaction conditions is also increased (Table 1). In the reactions examined, only the *E* vinyl phosphonates were formed. More importantly, it was shown, using a non-racemic allylic hydroxy phosphonate that the palladium(0)-catalyzed addition of dibenzylamine preceded with complete chirality transfer. A sample of hydroxy phosphonate **2b** was prepared in 97% e.e. (S isomer) [13]. Formation of the carbonate **5b** and palladium(0)-catalyzed addition of dibenzylamine (Table 1, entry 1) gave γ-amino vinyl phosphonate (R = Bn) with >95% e.e. by HPLC.

Having identified successful reaction conditions for the intermolecular addition of amines, our attention turned to the intramolecular addition of pendent amines [14] as a route to non-racemic pyrrolidines and piperidines (Scheme 5). Surprisingly, treatment of amine **5e** with $Pd(PPh_3)_4$ in THF at room temperature lead to the formation both the *E* and *Z* vinyl phosphonates **12a** and **12b** in a 1:1.8 ratio (Entry 3, Table 2). Furthermore, as the reaction temperature decreased the amount of *Z* isomer **12b** increased (Entries 1 and 2). Conversely, as the temperature increased the *E* alkene **12a** became the predominant isomer (Entry 4). It was also observed that at higher temperatures the *Z* isomer **12b** could be converted to *E* isomer **12a** under the reaction conditions. Similarly, reaction of the amine **5f** with $Pd(PPh_3)_4$ at −15 °C gave the piperidine vinyl phosphonate also as a mixture of *E* and *Z* isomers **14a** and **14b** (1:3.9). The *E* and *Z* isomers are distinguished by the H–H and P–H couplings of the vinyl protons in the ^{1}H NMR spectra. In particular, H-2 of the *Z*-vinyl phosphonates **12b/14b** exhibit a *trans* P–H coupling constant of 53–56 Hz, whereas H-2 of the *E*-vinyl phosphonates **12a/14a** show a *cis* P–H coupling constant of 22–24 Hz [5].

Table 1
Palladium(0)-catalyzed intermolecular allylic amination

Entry	S.M. #	R^1	Prod. #	Amine, $N(R^2)_2$	Yield (%)
1	**5b**	Ph	**11aa**	$N(CH_2Ph)_2$	95
2	**5b**	Ph	**11ab**	$N(CH_2CH_3)_2$	74
3	**5b**	Ph	**11ac**	$N(CH_2CH_2)_2O$	75
4	**5c**	Me	**11ba**	$N(CH_2Ph)_2$	98
5	**5c**	Me	**11bb**	$N(CH_2CH_3)_2$	64
6	**5c**	Me	**11bc**	$N(CH_2CH_2)_2O$	78

We and others have observed the formation of varying amounts of the *Z* vinyl phosphonate isomer in the intermolecular addition of other types of nucleophile [5b,5c,8,9]. The *E*/*Z* ratios seem to depend upon both the type of nucleophile and the reactions conditions, with less reactive nucleophiles giving increasing amounts of the *Z* isomer. The results (Scheme 5 and Table 2) can be rationalized (Scheme 6) by the intermediacy of equilibrating palladium species [5c]. The initially formed *syn*,*syn* π-allyl can undergo nucleophilic attack to generate the *E* vinyl phosphonate **12a**. Alternatively, an η^3–η^1 rearrangement, Cα–Cβ bond rotation, and η^1–η^3 rearrangement would give the *syn*,*anti* π-allyl. Attack of the nucleophile on the *syn*,*anti* π-allyl would generate the *Z* vinyl phosphonate **12b**. The temperature dependence of this process and the conversion of **12b** to **12a**, suggests that amine addition is reversible and that **12a** is the thermodynamic product and **12b** is the kinetic product. A further consequence of the proposed mechanism is that **12a** and **12b** would possess the opposite configuration at Cα. Indeed, when starting amine **5e** with 73% e.e. was subjected to the reaction conditions, the products **12a** and **12b** were isolated with 60% e.e. and 73% e.e., respectively. Reduction of **12a** and **12b** led to the formation of the enantiomers of saturated phosphonate **13**.



Scheme 5.

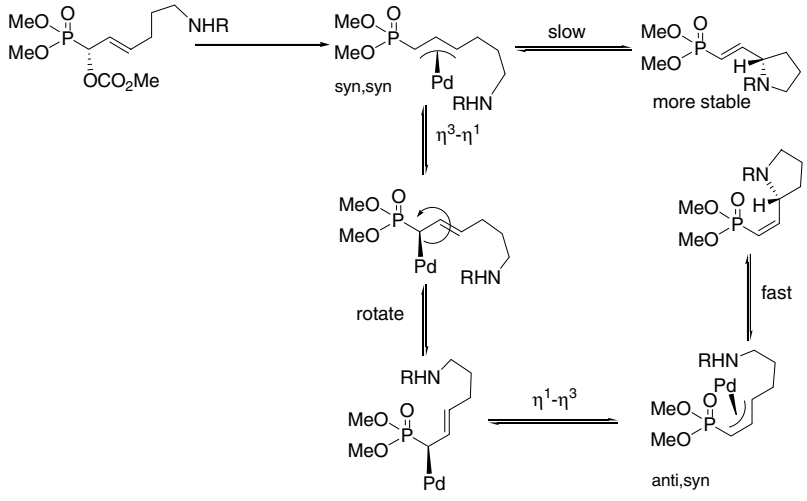
Table 2
Palladium(0)-catalyzed intramolecular allylic amination

Entry	SM	Temp (°C)	Yield (%)	*E*:*Z* ratio
1	**5e**	−15	71	1:8.5
2	**5e**	0	66	1:3.2
3	**5e**	25	70	1:1.8
4	**5e**	45	82	>20:1
5	**5f**	−15	74	1:3.9

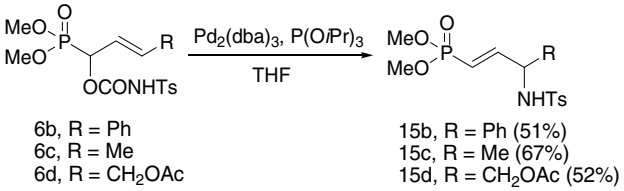
2.3. Palladium(0)-catalyzed decarboxylative rearrangement of tosyl carbamates

In some related work, we have shown that acetoacetate esters of allylic hydroxy phosphonates undergo a palladium(0)-catalyzed decarboxylative rearrangement (Carroll rearrangement) to yield carbon-substituted vinyl phosphonates with retention of configuration [15]. Since tosyl amides are viable nucleophiles for reaction with palladium π allyl complexes [16], it appeared that toysl carbamates should also undergo decarboxylative rearrangement to yield γ-tosylamido vinyl phosphonates.

The reaction of allylic phosphonates **6b–d** with $Pd_2(dba)_3$ and $P(OiPr)_3$ in THF resulted in the exclusive formation of *E* γ-tosylamido vinyl phosphonates (Scheme 7). The reaction was complete after stirring for 1 h at room temperature and the color of the solution changed from purple to green. The products were obtained as white crystalline solids after purification. Interestingly, attempts



Scheme 6.



Scheme 7.

using $Pd(OAc)_2/PPh_3$ or $Pd_2(dba)_3$/dppe as the palladium (0) sources were not successful and no reaction was observed. Furthermore, when hydroxy phosphonate **2b** with 80% e.e. was converted to the tosyl carbamate **6b** and treated as described above, the product tosyl amide **15b** was recovered with 80% e.e., demonstrating the reaction proceeds with chirality transfer. Tosyl amide **15d** was studied using single crystal X-ray diffraction. The X-ray crystal structure of **15d** revealed the expected *trans* alkene geometry with a H–Cα–Cβ-H dihedral angle of 178.7° (see Fig. 1, Tables 3 & 4).

The transformation of **6b–d** to **15b–d** can be rationalized by a Pd(0)-catalyzed cleavage of the allylic carbamate and π-allyl formation, followed by decarboxylation and nucleophilic attack by the resulting tosyl amide anion on the π-allyl. The reaction of difunctional substrate **6d** is particularly remarkable, since in theory, either the tosyl carbamate or the acetate could act as leaving groups generating two different of π-allylpalladium intermediates.

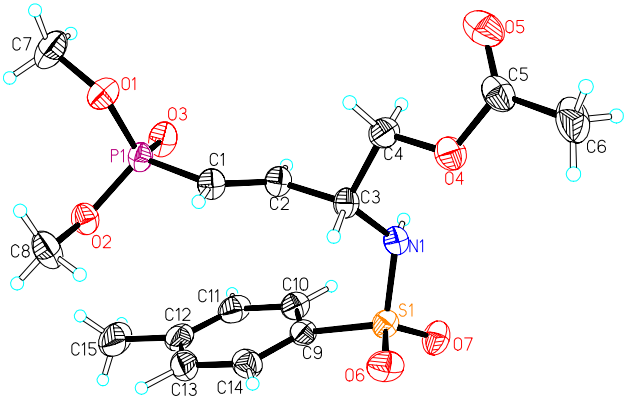


Fig. 1. Projection view of the vinyl phosphonate **15d** with 50% thermal ellipsoids.

2.4. Palladium(II)-catalyzed reactions

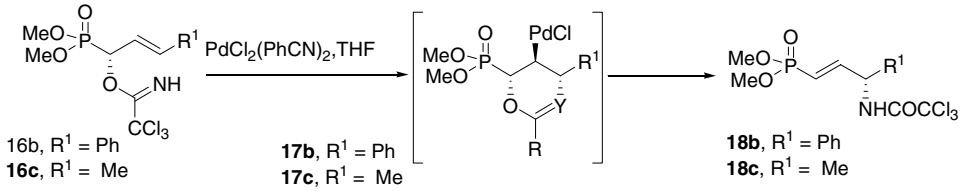
A further aim of this project was the introduction of nitrogen substituents at the β carbon with additional functionality at the γ or δ positions as a handle for further manipulation and chain elongation. This can conceivably be achieved by introducing a pendent nitrogen nucleophile at the α-position and inducing a regioselective nucleophile attack on the alkene mediated by an electrophile.

We and others have previously reported that allylic hydroxy phosphonates react with trichloroacetonitrile and DBU to give the corresponding trichloroacetimidates **16** [5e,17]. The imidates **16** were reported by Öhler [17] to rearrange upon heating. We showed that the trichloroacetimidates **16** reacted with NBS in $CHCl_3$ solution at room temperature to give vinyl phosphonates **18** [5e]. Not surprisingly, treatment of the imidates **16** with $Pd(PhCN)_2Cl_2$ in THF also gave the γ-amido vinyl phosphonates **18** in good yield (see Scheme 8).

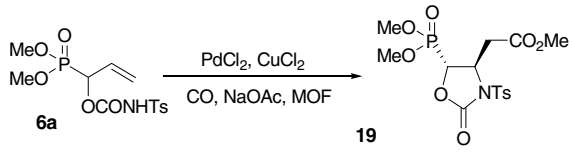
The results observed with both the Pd(II) and Br^+ catalyzed reactions are consistent with a mechanism previously proposed for metal-ion catalyzed [3.3] rearrangements [18]. Coordination of the metal ion [18] (or bromonium ion [19]) to the alkene leads nucleophilic attack of the nitrogen nucleophile on the γ carbon giving an intermediate oxazine **17**. Elimination of the palladium(II) (or bromine) and the oxygen atom across Cα and Cβ leads to the γ-substituted vinyl phosphonate. Clearly, in order to install a nitrogen substituent at the β-position a nucleophile with a different geometry will be required. Fortunately, tosyl carbamates (and other carbamates) have been shown to participate in range of palladium(II) induced cyclization reactions [20–22]. The eventual fate of the organopalladium intermediates depend upon product structure and reaction conditions. Examples of carbonylative trapping with CO [20], β-hydride elimination [21] and β-heteroatom elimination [22] have been reported. All of these reactions would ultimately fulfill our requirements.

2.5. Intramolecular aminopalladation and carbonylation

The allylic carbamate **6a** underwent intramolecular aminocarbonylation in the presence of palladium(II) chloride, copper(II) chloride, sodium acetate and methyl



Scheme 8.



Scheme 9.

orthoformate in methanol under a carbon monoxide atmosphere (balloon) to provide the oxazolidinone **19** (see Scheme 9). The structure of oxazolidinone **19** was assigned using NMR spectroscopy and X-ray crystallography. The ^{31}P NMR spectrum of the crude product exhibited only one new signal, which implies that only one diastereomer was formed. The ^{1}H NMR spectra of the oxazolidinone **19** exhibited a doublet of doublets at 4.5 ppm, which corresponded to the Cα–H. The calculated Cα–H to Cβ–H and Cα–H to P coupling constant values were approximately 3.6 and 1.0 Hz, respectively. The small P–H coupling constant value is typical for α-protons for phosphonate substituents on five-membered rings [6b]. The *trans*-stereochemistry of the oxazolidinone was assigned by X-ray crystallography (Fig. 2, Tables 3 & 5) with an observed H–Cα–Cβ–H dihedral angle of 110.2°.

2.6. Intramolecular aminopalladation and β-heteroatom elimination

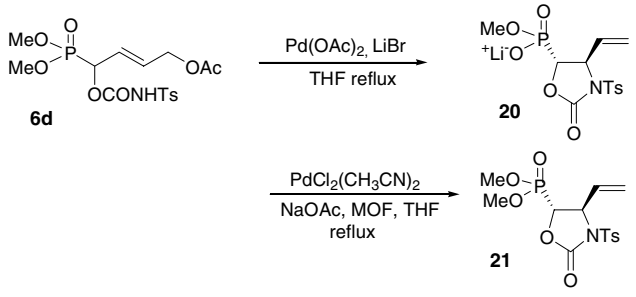
It was shown above that treatment of allylic carbamate **6d** with palladium (0) led to the formation of a γ-tosylamido vinyl phosphonate **15d**. However, a different reaction pathway is observed with palladium (II) compounds. Treatment of allylic carbamate with $Pd(OAc)_2$ and LiBr in THF for 3 h at reflux (Scheme 10) yielded the water soluble lithium salt **20**. The ^{31}P NMR spectrum of the crude aqueous layer exhibited one signal at 15.0 ppm and the ^{1}H NMR spectrum indicated the presence of a terminal alkene and only one phosphonate methoxy signal. The cleavage of the phosphonate methyl esters with halide ion is well precedented. Therefore, an alternative method for the desired transformation was investigated. The tosyl carbamate was treated with $PdCl_2(CH_3CN)_2$ with sodium acetate as the base in a solution of trimethyl orthoformate and THF to give the oxazolidinone **21**.

The oxazolidinone **21** was characterized using NMR spectroscopy. The ^{31}P NMR spectrum of the product exhibited only one signal at 17.6 ppm. The ^{1}H NMR spectrum showed a signal for the Cα–H at 4.29 ppm with a Cα–H to Cβ–H coupling constant of 3.8 Hz. The Cα–H to Cβ–H coupling constant was close to that observed for oxazolidinone **19**, suggesting that the substituents on oxazolidinone **21** are also *trans*.

Catalysis by palladium (II) species begins with palladium coordinating to the alkene inducing a nucleophilic attack of the tosyl carbamate anion on the alkene forming an organopalladium intermediate. The carbon–palladium bond is cleaved with accompanying β-heteroatom elimination, as opposed to the more common β-hydride elimination, resulting in regeneration of the palladium (II) catalyst and therefore no additional oxidant is required.

2.7. Intramolecular aminopalladation and β-hydride elimination

Alternatively, an alkene can be formed by a β-hydride elimination in Wacker type reaction. Although potentially this could be quite efficient, this process requires a stoichiometric quantity of a terminal oxidizing agent to reoxidize the palladium (0) to palladium (II). *N*-Tosyl carbamate **6c** was treated with $Pd(OAc)_2/Cu(OAc)_2$ with NaOAc in DMF/THF solution to yield a mixture comprising of oxazolidinone **21** (28%), the γ-tosyl amide **15c**



Scheme 10.

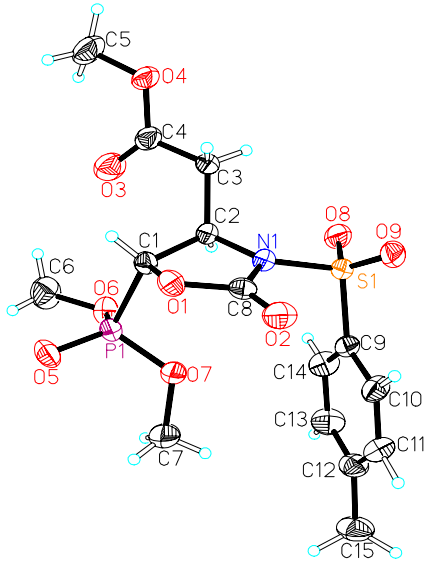
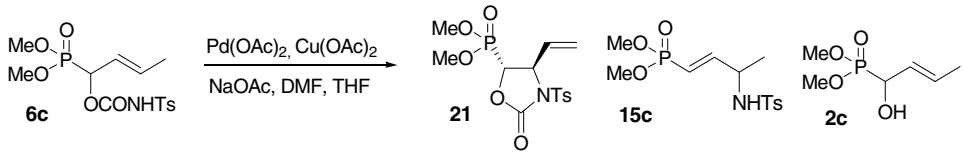


Fig. 2. Projection view of oxazolidinone **19** view with 50% thermal ellipsoids.



Scheme 11.

(20%), hydroxy phosphonate **2c** (5%) and the starting carbamate **6c** (47%) (Scheme 11).

In summary, with the judicious selection of nitrogen nucleophile and palladium catalyst, β and γ substituted amino phosphonates can be formed with excellent regio- and stereochemical control.

3. Experimental

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at 300, 75 and 121 MHz, respectively, in $CDCl_3$. ^{1}H NMR spectra are referenced to internal tetramethylsilane (TMS, $\delta = 0.00$), ^{13}C NMR spectra to the center-line of $CDCl_3$ (77.23 ppm) and ^{31}P NMR spectra to external 85% H_3PO_4. Coupling constants, J, are reported in Hz. Enantiomer ratios were measured by chiral stationary-phase HPLC on a (*S*,*S*)-Whelk-O 1 column or a Chiralpak AS column (10% or 20% EtOH in hexane, 1 mL/min, 210 or 254 nm detection) or by ^{1}H NMR using Karfarski's quinine method [11b]. Optical rotations were determined using a polarimeter set at 589 nm. The following compounds were prepared using published procedures (±) and (1R) (70% e.e.) dimethyl-[1-hydroxy-2-propenyl]phosphonate (**2a**) [5b], (±) and (1*R*) (98% e.e.) (2*E*)dimethyl-(1-hydroxy-3-phenyl-2-propenyl) phosphonate (**2b**) [1a,13,5b] (±)(2*E*)dimethyl-(1-hydroxy-2-butenyl)phosphonate (**2c**) [1a,5c], dimethyl-[1-(methoxycarbonyloxy)-2-propenyl]phosphonate (**5a**) [5b], (2*E*)dimethyl-[1-(methoxycarbonyloxy)-3-phenyl-2-propenyl]phosphonate (**5b**) [5b], and (2*E*)dimethyl-[1-(methoxycarbonyloxy)-2-butenyl]phosphonate (**5c**) [5c].

3.1. cis-4-Acetoxy-2-buten-1-ol (*4*)

To a stirred suspension of polyvinylpyridine (1.53 g, 14.6 mmol) and acetyl chloride (864 μL, 12.2 mmol) in acetonitile at 0 °C, was added *cis*-2-butene-1,4-diol (**3**) (1 mL, 12.1 mmol). After the reaction was complete (TLC), the mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc:hexanes, 1:1) to give alcohol **4** as a colorless liquid (60%). IR (NaCl, neat) 3378, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.84 (1H, m), 5.65 (1H, m), 4.68 (2H, d, $J = 6.5$ Hz), 4.26 (2H, d, $J = 6.6$ Hz), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$) δ 171.6, 133.8, 125.9, 60.5, 58.8, 21.4.

3.2. trans-4-Acetoxy-2-buten-1-al (*1d*)

To a stirred suspension of PCC (2.36 g, 10.95 mmol) and Celite® (2.30 g) in anhydrous CH_2Cl_2 at room temperature was added a solution of *cis*-4-acetoxy-2-buten-1-ol (**4**) (950 mg, 7.30 mmol) in CH_2Cl_2. The resulting mixture was stirred until the reaction was complete (TLC). The mixture was diluted with Et_2O and filtered through a pad of Florisil® and Celite. The filtrate was concentrated in vacuo to give a green liquid, which was purified by column chromatography (SiO_2, EtOAc;hexanes, 9:1) to give aldehyde **1d** as a light yellow liquid (61%). IR (NaCl, neat) 1745, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.56 (1H, d, $J = 7.8$ Hz), 6.80 (1H, dt, $J = 4.3$, 15.8 Hz), 6.24 (1H, m), 4.83 (2H, dd, $J = 1.8$, 4.3 Hz), 2.11 (3H, s); ^{13}C NMR ($CDCl_3$) δ 192.9, 170.3, 149.6, 132.3, 62.5, 20.7.

3.3. N-(Methyl 2-acetate)-5-amino-1-pentene (*9a*)

4-Pentenal **8a** (1.0 g, 11.9 mmol) was dissolved in MeOH (15 mL). Methyl glycine hydrochloride (2.98 g, 23.8 mmol) and sodium cyanoborohydride (0.374 g, 5.95 mmol) were added. The reaction mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ solution was added to adjust the pH to 8, and then resulting mixture was extracted with CH_2Cl_2 (4×50 mL). The combined extracts were dried and evaporated in vacuo. The crude product was purified by chromatography (SiO_2, hexane:EtOAc, 4:1) to give amine **9a** a colorless oil (1.29 g, 69%). IR (neat, NaCl) 3335, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.81 (1H, m), 4.96 (2H, m), 3.71 (3H, s), 3.39 (2H, s), 2.60 (2H, t, $J = 7.2$ Hz), 2.09 (2H, m), 1.58 (3H, m); ^{13}C NMR ($CDCl_3$) δ 173.2, 138.5, 114.9, 51.8, 51.0, 49.2, 31.5, 29; HRMS (FAB, MH^+) Calc. for $C_8H_{15}NO_2$: 158.1181. Found 158.1179.

3.4. N-(Tert-butoxycarbonyl)-N-(methyl 2-acetate)-5-amino-1-pentene (*10a*)

The amine **9a** (0.965 g, 6.14 mmol) was dissolved in MeOH (15 mL), then $(Boc)_2O$ (1.34 g, 6.14 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated in vacuo and the residue was purified by chromatography (SiO_2, hexane:EtOAc, 4:1) to give **10a** as a

colorless oil (0.854 g, 97%). IR (neat, NaCl) 1757, 1699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1H, m), 5.00 (2H, m), 3.96 (1H, s) 3.86 (1H, s), 3.73 (3H, s), 3.28 (2H, m), 2.05 (2H, m), 1.62 (2H, m), 1.47 & 1.42 (9H, s); ^{13}C NMR ($CDCl_3$) (reported as rotomer pairs) δ 170.9 and 170.8, 156.0 and 155.3, 138.2 and 138.1, 115.2 and 115.2, 80.3, 52.2, 49.5 and 48.9, 48.2 and 48.1, 31.1 and 31.0, 28.6 and 28.5, 27.8 and 27.5; HRMS (FAB, MH^+) Calc. for $C_{13}H_{24}NO_4$: 258.17053. Found 258.1706.

3.5. N-(Methyl 2-acetate)-6-amino-1-hexene (**9b**)

To a suspension of powdered molecular sieves (10 g) and Celite (10 g) in CH_2Cl_2 (80 mL) was added 5-hexen-1-ol **7** (4 g, 39.9 mmol). PCC (17.2 g) was added in small portions over a 10-min period. The reaction mixture was stirred at room temperature for 2 h, then it was filtered through Celite. The Celite was washed with Et_2O and the filtrate was concentrated in vacuo to give the crude aldehyde **8b**. The aldehyde was dissolved in MeOH (20 mL) and methyl glycine hydrochloride (7.932 g, 63.2 mmol) and sodium cyanoborohydride (0.992 g, 15.8 mmol) were added. Reaction mixture was stirred at room temperature for 24 h. Saturated $NaHCO_3$ solution was added to adjust the pH to 8 and the solution was extracted with CH_2Cl_2 (4×70 mL). The combined extracts were evaporated in vacuo and the crude product was purified by chromatography (SiO_2, hexane:EtOAc, 4:1) to give amine **9b** as a colorless oil (2.29 g, 34% over two steps). IR (neat, NaCl) 3330, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (1H, m), 4.97 (2H, m), 3.73 (3H, s), 3.42 (2H, s), 2.61 (2H, m), 2.07 (2H, m), 1.76 (1H, brd s), 1.48 (4H, m); ^{13}C NMR ($CDCl_3$) δ 173.2, 138.9, 114.8, 52.0, 51.0, 49.7, 33.8, 29.6, 26.7; HRMS (FAB, MH^+) Calc. for $C_9H_{18}NO_2$: 172.1338 Found 172.1338.

3.6. N-(Tert-butoxycarbonyl)-N-(methyl 2-acetate)-6-amino-1-hexene (**10b**)

To a solution of the amine **9b** (2.1g, 12.3 mmol) in MeOH (15 mL), was added $(Boc)_2O$ (2.94 g, 13.5 mmol). The reaction mixture was stirred at room temperature for 20 h. Et_3N (5 mL) was added and the resulting mixture was stirred for an additional 24 h. The solvent was evaporated in vacuo and the residue was purified by chromatography (SiO_2, hexane:EtOAc, 2:1) to give **10b** as a colorless oil (3.15 g, 95%). IR (neat, NaCl) 1757, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (1H, m), 4.96(2H, m), 3.94 (1H, s), 3.84 (1H, s), 3.72 (3H, s), 3.26 (2H, m), 2.06 (2H, m), 1.62 (2H, m), 1.44 (4H, m), 1.46 & 1.41 (9H, 2x s); ^{13}C NMR ($CDCl_3$) (reported as rotomer pairs) δ 170.9 and 170.8, 156.0 and 155.3, 138.8 and 138.7, 114.8 and 114.8, 80.3, 52.1 and 52.1, 49.3 and 48.7, 48.3 and 48.2, 33.6 and 33.5, 28.5 and 28.4, 27.9 and 27.7, 26.2 and 26.1; HRMS (EI, MH^+) Calc. for $C_{14}H_{26}NO_4$: 272.1862. Found 272.1840.

3.7. Preparation of racemic hydroxy phosphonates (**2a–d**)

Distilled $Ti(OiPr)_4$ (20 mol%) was added to a solution of dimethyl phosphite (2 equiv.) in freshly distilled CH_2Cl_2 at 0 °C. The solution was stirred for 30 min, then the aldehyde (1 equiv.) was added. When the reaction was complete, as indicated by TLC (SiO_2, EtOAc:hexane 1:1), the mixture was diluted further with CH_2Cl_2 and washed with H_2O. The layers were separated and the H_2O layer was re-extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated in vacuo to give the crude hydroxy phosphonates. Purification by column chromatography (SiO_2, gradient EtOAc:hexanes 1:1 to pure EtOAc) gave the pure α-hydroxy phosphonates.

3.8. Preparation of non-racemic hydroxy phosphonates (**2a–d**)

To a solution of dimethyl-L-tartrate (20 mol %) in freshly distilled Et_2O (total conc. = 0.07 M) was added distilled $Ti(OiPr)_4$ (20 mol%). The mixture was stirred at −15 °C for 30 min to insure complete complexation. The aldehyde (40 mmol) was added and the mixture was stirred for an additional 15 min. Dimethyl phosphite (80 mmol) was added and the reaction mixture was placed in the freezer (approx. −15 °C). After the reaction was completed, as indicated by TLC (SiO_2, EtOAc:hexane, 1:1), the reaction mixture was treated with deionized H_2O and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give crude product. Purification by column chromatography (SiO_2, gradient EtOAc:hexanes, 1:1 to pure EtOAc) gave the pure α-hydroxy phosphonates.

3.9. Dimethyl-(1-hydroxy-4-acetoxy-2E-butenyl) phosphonate (**2d**)

Pale yellow oil (60%). IR (neat, NaCl) 3299, 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.01 (2H, m), 4.57 (3H, m), 3.82 (6H, d, J_{HP} = 10.4 Hz), 2.08 (3H, s); ^{13}C NMR ($CDCl_3$) δ 171.1, 128.6, 127.5 (d, J_{CP} = 12.7 Hz), 68.8 (d, J_{CP} = 161 Hz), 64.4, 54.3 (d, J_{CP} = 6.9 Hz), 54.1 (d, J_{CP} = 7.4 Hz), 21.3; ^{31}P NMR ($CDCl_3$) δ 24.6.

3.10. Dimethyl [N-(methyl 2-acetate)-6-amino-1-(methoxycarbonyloxy)-2-hexenyl] phosphonate (**5e**)

To solution of phosphonate **5a** (1.34 g, 5.98 mmol) and alkene **10a** (0.770 g, 2.99 mmol) in toluene (5 mL) was added Grubbs second generation catalyst (0.123 g,

0.150 mmol). The reaction flask was placed in a preheated oil bath, and the reaction mixture was stirred at 75 °C for 12 h. An additional of catalyst (0.062 g, 0.075 mmol) was added to the reaction mixture for stirred for a further 24 h at 75 °C. The reaction mixture was filtered through a plug of SiO_2 with acetone (150 mL). The filtrate was concentrated in vacuo and then the residue was dissolved in CH_2Cl_2 (5 mL) and TFA (5 mL). The mixture was stirred at room temperature for 3 h and then it was diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and combined extracts were dried and evaporated in vacuo. The brown oily residue was purified by chromatography (SiO_2, gradient hexane:EtOAc, 1:1 to EtOAc to acetone) give phosphonate **5e** as a colorless oil (0.785 g, 74%). IR (neat, NaCl) 3330,1753 cm^{-1}, ^1H NMR ($CDCl_3$) δ 5.92 (1H, m), 5.57 (1H, m), 5.40 (1H, dd, $J_{HH} = 7.7$ Hz, $J_{HP} = 12.7$ Hz), 3.78 (3H, s), 3.77 (3H, d, $J_{HP} = 10.6$ Hz), 3.76 (3H, d, $J_{HP} = 10.6$ Hz), 3.69 (3H, s), 3.37 (2H, s), 2.57 (2H, t, $J_{HH} = 7.1$ Hz); 2.13 (2H, m), 1.98 (1H, s), 1.57 (2H, m); ^{13}C NMR ($CDCl_3$) δ 173.0, 154.9 (d, $J_{CP} = 9.9$ Hz), 138.1 (d, $J_{CP} = 12.5$Hz), 121.0, 73.1 (d, $J_{CP} = 171$ Hz), 55.5, 54.0 (d, $J_{CP} = 7.1$ Hz), 53.9 (d, $J_{CP} = 6.5$ Hz), 52.0, 50.8, 49.0, 30.2, 29.0 (d, $J_{CP} = 2.3$ Hz); ^{31}P NMR ($CDCl_3$) δ 20.3; HRMS (FAB, MH^+) Calc. for $C_{13}H_{25}O_8NP$: 354.1318 Found 354.1312.

3.11. Dimethyl [N-(methyl 2-acetate)-7-amino-1-(methoxycarbonyloxy)-2-heptenyl] phosphonate (*5f*)

To a solution of phosphonate **5a** (1.47 g, 6.56 mmol) and alkene **10b** (0.89 g, 3.28 mmol) in toluene (8 mL) was added Grubbs second generation catalyst (0.135 g, 0.164 mmol). The reaction flask was placed in a preheated oil bath and the reaction mixture was stirred at 75 °C for 2 days. An additional portion of catalyst (0.068 g, 0.082 mmol) was added to the reaction mixture, and stirring was continued stirring for a further 24 h. The reaction mixture was filtered through a plug of SiO_2 with acetone (150 mL). The filtrate was concentrated in vacuo, then the residue was dissolved in CH_2Cl_2 (5 mL) and TFA (5 mL) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL) and combined extracts were dried and evaporated in vacuo. The brown oily residue was purified by chromatography (SiO_2, gradient hexane:EtOAc, 1:1 to EtOAc to acetone) give phosphonate **5f** as a colorless oil (0.699 g, 58%). IR (neat, NaCl) 3330,1753 cm^{-1}, ^1H NMR ($CDCl_3$) δ 5.94 (1H, m), 5.56 (1H, m), 5.43 (1H, dd, $J_{HH} = 7.9$ Hz, $J_{HP} = 12.4$ Hz), 3.81 (3H, s), 3.80 (3H, d, $J_{HP} = 10.6$ Hz), 3.79 (3H, d, $J_{HP} = 10.6$ Hz), 3.72 (3H, s), 3.40 (2H, s), 2.59 (2H, t, $J_{HH} = 6.8$ Hz); 2.12 (2H, m), 1.72 (1H, s), 1.47 (4H, m); ^{13}C NMR ($CDCl_3$) δ 173.1, 154.9 (d, $J_{CP} = 9.7$ Hz), 138.6 (d, $J_{CP} = 12.4$ Hz), 120.7 (d, $J_{CP} = 3.8$ Hz), 73.2 (d, $J_{CP} = 171$ Hz), 55.5, 54.0 (d, $J_{CP} = 7.1$ Hz), 53.9 (d, $J_{CP} = 6.4$ Hz), 51.9, 50.9, 49.5, 32.4 (d, $J_{CP} = 0.9$ Hz), 29.6, 26.3 (d, $J_{CP} = 2.3$ Hz); ^{31}P NMR ($CDCl_3$) δ 20.4; HRMS (FAB, MH^+) Calc. for $C_{13}H_{25}O_8NP$: 368.1474. Found 368.1468.

3.12. General procedure for synthesis of dimethyl (3-amino-1-alkenyl) phosphonates (*11*) via palladium-catalyzed intermolecular addition of amine nucleophiles

Triphenylphosphine (0.066 g, 0.252 mmol) and $Pd(OAc)_2$ (0.014 g, 0.063 mmol) were dissolved in THF (2 mL) and the resulting solution was stirred for 30 min. A solution of the allylic carbonate **5** (1.26 mmol) in THF (1 mL) was added to the reaction mixture, followed by the addition of secondary amine (2.52 mmol) and the reaction mixture was heated to reflux for 1–2 h. When the reaction was complete as indicated by ^{31}P NMR, the mixture was concentrated in vacuo and the resulting yellow oil was purified by column chromatography (SiO_2, $CHCl_3$:MeOH gradient). Isolated yields and physical data for compounds **11** are given below.

3.13. Dimethyl [3-(N,N-dibenzylamino)-3-phenyl-1-propenyl] phosphonate (*11aa*)

95% yield, an oil. ^1H NMR ($CDCl_3$) δ 7.41–7.23 (15H, m) 7.11 (1H, ddd, $J_{HH} = 17.3$, 7.3 Hz, $J_{HP} = 25$ Hz), 5.88 (1H, ddd, $J_{HH} = 17.3$, 1.4 Hz, $J_{HP} = 21$ Hz), 4.45 (1H, dd, $J_{HH} = 7.3$, 1.3 Hz), 3.79 (3H, d, $J_{HP} = 10.6$ Hz), 3.75 (3H, d, $J_{HP} = 10.6$ Hz), 3.61 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 151.9 (d, $J_{CP} = 4.8$ Hz), 138.9 138.5, 128.7, 128.6, 128.5, 127.7, 127.2, 119.6 (d, $J_{CP} = 185$ Hz), 65.2 (d, $J_{CP} = 22.8$ Hz), 54.1, 52.7 (d, $J_{CP} = 5.6$ Hz); 52.6 (d, $J_{CP} = 5.6$ Hz); ^{31}P NMR δ 20.7. Anal. Calc. for $C_{25}H_{28}PO_3N$: C, 71.23; H, 6.70. Found: C, 70.96; H, 6.75%.

3.14. Dimethyl [3-(N,N-diethylamino)-3-phenyl-1-propenyl] phosphonate (*11ab*)

75% yield, an oil. ^1H NMR ($CDCl_3$) δ 7.26–7.10 (5H, m), 6.84 (1H, ddd, $J_{HH} = 17.2$, 8.1 Hz; $J_{HP} = 25.3$ Hz), 5.75 (1H, dd, $J_{HH} = 17.3$ Hz; $J_{HP} = 21$ Hz), 4.22 (1H, d, $J_{HH} = 8.1$ Hz), 3.69 (3H, d, $J_{HP} = 10.8$ Hz) 3.66 (d3H,, $J_{HP} = 11.2$ Hz), 2.48 (4H, q, $J_{HH} = 7.0$ Hz), 0.98 (6H, t, $J_{HH} = 7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 154 (d, $J_{CP} = 4.5$ Hz), 140.3, 128.6, 128.2, 127.6, 116. 6 (d, $J_{CP} = 186$ Hz), 69.2 (d, $J_{CP} = 21.7$ Hz), 52.5 (d, $J_{CP} = 5.6$ Hz); 52.5 (d, $J_{CP} = 6$ Hz), 43.4, 12.1; ^{31}P

NMR δ 20.9. Anal. Calc. for $C_{15}H_{24}PO_3N$: C, 60.58; H, 8.14. Found: C, 60.51; H, 8.14%.

3.15. Dimethyl {3-(1-morpholinyl)-3-phenyl-1-propenyl} phosphonate (**11ac**)

74% yield, an oil. ^{1}H NMR ($CDCl_3$) δ 7.33–7.31 (2H, m), 7.29–7.26 (3H, m), 6.85 (1H, ddd, J_{HH} = 17.1, 8.1 Hz, J_{HP} = 25.3 Hz), 5.86 (1H, dd, J_{HH} = 17.2 Hz, J_{HP} = 20.3 Hz), 3.75 (m, 5H), 3.7 (3H, d, J_{HP} = 11.0 Hz), 3.65 (3H, d, J_{HP} = 11.1 Hz), 2.39 (m, 4H); ^{13}C NMR 153.9 (d, J_{CP} = 4.9 Hz), 139.2, 128.9, 128.4, 128.1, 117.2 (d, J_{CP} = 186 Hz), 74.8 (d, J_{CP} = 22.3Hz), 67.2, 52.6 (d, J_{CP} = 5.7 Hz), 52.5 (d, J_{CP} = 5.7 Hz), 52.1; ^{31}P NMR δ 21.0. Anal. Calc. for $C_{15}H_{22}PO_4N$: C, 57.85; H, 7.13. Found: C, 57.55; H, 7.03%.

3.16. Dimethyl [3-(N,N-dibenzylamino)-1-butenyl] phosphonate (**11ba**)

98% yield, an oil. ^{1}H NMR ($CDCl_3$) δ 7.37–7.18 (10H, m), 6.9 (1H, ddd, J_{HH} = 17.4, 5.3 Hz; J_{HP} = 22.6 Hz), 5.76 (1H, ddd, J_{HH} = 17.4, 1.7 Hz; J_{HP} = 20.8 Hz), 3.69 (3H, d, J_{HP} = 11 Hz), 3.67 (3H, d, J_{HP} = 11 Hz), 3.57 (4H, s), 3.48 (1H, m) 1.18 (3H, d, J_{HH} = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 154.9 (d, J_{CP} = 3.8 Hz), 139.1, 127.9, 127.6, 126.4, 115.9 (d, J_{CP} = 185 Hz), 54.6 (d, J_{CP} = 21 Hz), 54.5, 51.82 (d, J_{CP} = 5.9 Hz), 51.75 (d, J_{CP} = 5.9 Hz), 13.2; ^{31}P NMR δ 22.0. Anal. Calc. for $C_{20}H_{26}PO_3N$: C, 66.82; H, 7.26. Found: C, 67.08; H, 7.26%.

3.17. Dimethyl [3-(N,N-diethylamino)-1-butenyl] phosphonate (**11bb**)

78% yield, an oil. ^{1}H NMR ($CDCl_3$) δ 6.8 (1H, ddd, J_{HH} = 17.3, 6.0 Hz; J_{HP} = 23.3 Hz), 5.75 (1H, ddd, J_{HH} = 17.3, 1.4 Hz; J_{HP} = 21.2 Hz), 3.73 (6H, d, J_{HP} = 11.1 Hz), 3.41 (1H, m), 2.42 (4H, m), 1.18 (3H, d, J_{HH} = 6.6 Hz), 1.05 (6H, t, J = 7.1 Hz); ^{13}C NMR (CDCl3) 156.8 (d, J_{CP} = 3.9 Hz), 115.6 (d, J_{CP} = 186 Hz), 57.8 (d, J_{CP} = 21.3 Hz), 52.6 (d, J_{CP} = 5.6 Hz), 52.5 (d, J_{CP} = 5.6 Hz), 44.0, 15.7, 13.9; ^{31}P NMR δ 21.5. Anal. Calc. for $C_{10}H_{22}PO_3N$: C, 51.03; H; 9.35. Found: C, 51.02; H, 9.00%.

3.18. Dimethyl [3-morpholine-1-butenyl] phosphonate (**11bc**)

64% yield, an oil. ^{1}H NMR($CDCl_3$) δ 6.74 (1H, ddd, J_{HH} = 17.2, 7.0 Hz; J_{HP} = 22.1 Hz), 5.8 (1H, ddd, J_{HH} = 17.3, 2.3 Hz; J_{HP} = 20.8 Hz); 3.75 (3H, d, J_{HP} = 11.4 Hz); 3.73 (3H, d, J_{HP} = 10.5 Hz), 3.70 (m, 4H), 3.11 (m, 1H), 2.51 (4H, m), 1.21 (3H, m); ^{13}C NMR ($CDCl_3$) δ 154.8 (d, J_{CP} = 4.1 Hz), 116.4 (d, J_{CP} = 186 Hz), 66.9, 62.5 (d, J_{CP} = 21.6 Hz), 52.2 (d, J_{CP} = 6 Hz), 52.1 (d, J_{CP} = 6 Hz), 50.0, 15.7; ^{31}P NMR δ 20.8.

3.19. Palladium-catalyzed Intramolecular addition of Amine Nucleophile to give (E) and (Z)-methyl 2-(2-(2-(dimethoxyphosphoryl)vinyl)pyrrolidin-1-yl)acetate (**12a**) and (**12b**)

To a solution of phosphonate **5e** (0.187 g, 0.529 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (0.031 g, 0.0256 mmol). The resulting solution was placed in a freezer (−15 °C) for 3 days. The reaction mixture was filtered through a plug of silica gel with acetone (150 mL). The filtrate was concentrated in vacuo and the yellow oily residue was purified by chromatography (SiO_2, gradient hexane:EtOAc, 1:1 to EtOAc) to give a mixture of cis and trans vinyl phosphonates **12** as a pale yellow oil (0.104 g, 71%). Further careful chromatography gave the pure *cis* vinyl phosphonate **12b**; ^{1}H NMR ($CDCl_3$) δ 6.44 (1H, ddd, J_{HH} = 13.1, 9.6 Hz, J_{HP} = 52.6 Hz), 5.67 (1H, ddd, J_{HH} = 13.1, 0.8 Hz, J_{HP} = 18.6 Hz), 3.87 (1H, m), 3.74 (3H, J_{HP} = 11.2 Hz), 3.72 (3H, J_{HP} = 11.2 Hz), 3.71 (3H, s), 3.53 (1H, d, J_{HH} = 16.8 Hz), 3.33 (1H, m), 3.17 (1H, d, J_{HH} = 16.8 Hz), 2.41 (1H, m), 2.07 (1H, m), 1.89 (2H, m), 1.64 (1H, m); ^{13}C NMR ($CDCl_3$) δ 171.7, 156.0 (d, J_{CP} = 4.0 Hz),, 117.3 (d, J_{CP} = 184 Hz), 63.3 (d, J_{CP} = 8.2 Hz), 55.1, 54.3, 52.3 (d, J_{CP} = 5.6 Hz), 52.2 (d, J_{CP} = 5.6 Hz), 51.8, 31.5 (d, J_{CP} = 2.1 Hz), 23.3; ^{31}P NMR ($CDCl_3$) δ 19.7; HRMS (FAB, NBA, M^+) Calc. for $C_{11}H_{20}O_5NP$: 277.1079 Found 277.1078; and the pure *trans* vinyl phosphonate **12a**; ^{1}H NMR ($CDCl_3$) δ 6.67 (1H, ddd, J_{HH} = 17.1, 7.2 Hz, J_{HP} = 24.3 Hz), 5.67 (1H, ddd, J_{HH} = 17.1, 0.6 Hz, J_{HP} = 21.2 Hz), 3.74 (3H, d, J_{HP} = 10.9 Hz), 3.73 (3H, d, J_{HP} = 10.9 Hz), 3.72 (3H, s), 3.49 (1H, d, J_{HH} = 16.8 Hz), 3.27 (2H, m), 3.19 (1H, d, J_{HH} = 16.8 Hz), 2.54 (1H, m), 2.11 (1H, m), 1.87 (2H, m), 1.69 (1H, m); ^{13}C NMR ($CDCl_3$) δ 171.1, 153.9, 117.4 (d, J_{CP} = 188 Hz), 66.5 (d, J_{CP} = 23.1 Hz), 53.9, 53.7, 52.7 (d, J_{CP} = 6.6 Hz), 52.6 (d, J_{CP} = 6.6 Hz), 51.9, 31.7 (d, J_{CP} = 1.4 Hz), 23.3; ^{31}P NMR ($CDCl_3$) δ 21.5; HRMS (EI, M^+) Calc. for $C_{11}H_{20}O_5NP$: 277.1079. Found 277.1077.

3.20. Methyl 2-(2-(2-(dimethoxyphosphoryl)-ethyl)pyrrolidin-1-yl)acetate (**13**)

To solution of the vinyl phosphonate **12a** (or **12b**) (0.130 g, 0.469 mmol) in MeOH (4 mL) was added a suspension of $KCO_2N{=}NCO_2K$ (1.37 g, 7.03 mmol). AcOH (1.13 g, 18.8 mmol) in MeOH (1 mL) was added to the stirred mixture slowly (over 4 h) via a syringe pump. After the addition was complete, the mixture was stirred for an additional hour and then the solvent was evaporated in vacuo. The residue was dissolved in

water, neutralized with saturated $NaHCO_3$ solution then extracted with CH_2Cl_2. The extracts were dried and evaporated in vacuo. The oily residue was purified by chromatography (SiO_2, hexane:EtOAc, 1:1 to EtOAc to acetone) to give the saturated phosphonate **13** as a colorless oil (0.118 g, 90%). IR (neat, NaCl) 1739.8 cm^{-1}, ^1H NMR ($CDCl_3$) δ 3.73 (3H, J_{HP} = 10.7 Hz), 3.72 (3H, J_{HP} = 10.7 Hz), 3.71 (3H, s), 3.55 (1H, d, J_{HH} = 16.6 Hz), 3.21 (1H, m), 3.17 (1H, d, J_{HH} = 16.6 Hz), 2.63 (1H, m), 2.43 (1H, m), 1.98–1.42 (8H, m); ^{13}C NMR ($CDCl_3$) δ 171.7, 63.2 (d, J_{CP} = 18.5), 54.48, 54.46, 52.6 (d, J_{CP} = 6.7 Hz), 52.5 (d, J_{CP} = 6.6 Hz), 51.8, 29.9, 26.2 (d, J_{CP} = 4.5), 23.0, 21.3 (d, J_{CP} = 141 Hz); ^{31}P NMR ($CDCl_3$) δ 35.9; HRMS (FAB, MH^+) Calc. for $C_{11}H_{23}O_5NP$: 280.1314. Found 280.1312.

3.21. Palladium-catalyzed Intramolecular addition of Amine Nucleophile to give (E) and (Z)-methyl 2-(2-(2-(dimethoxyphosphoryl)vinyl)piperidin-1-yl)acetate (**14a**) and (**14b**)

To a solution of phosphonate **5f** (0.539 g, 1.47 mmol) in THF (5 mL) was added $Pd(PPh_3)_4$ (0.0848 g, 0.0734 mmol). The resulting solution was placed in a freezer (−15 °C) for 24 h. The reaction mixture was filtered through a plug of silica gel with acetone (150 mL). The filtrate was concentrated in vacuo and the yellow oily residue was purified by chromatography (SiO_2, hexane:EtOAc, 1:1 to EtOAc) to give a mixture of cis and trans vinyl phosphonates **14** as a pale yellow oil (0.318 g, 74%). Further careful chromatography gave the pure *cis* vinyl phosphonate **14b**. IR (neat, NaCl) 1752 cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.43 (1H, ddd, J_{HH} = 13.2, 9.7 Hz, J_{HP} = 53 Hz), 5.60 (1H, ddd, J_{HH} = 13.3, 0.7 Hz, J_{HP} = 18.6 Hz), 3.68 (3H, d, J_{HP} = 11.1 Hz), 3.67 (3H, d, J_{HP} = 11.1Hz), 3.65 (3H, s), 3.61 (1H, m), 3.38 (1H, d, J_{HH} = 16.6 Hz), 2.99 (1H, d, J_{HH} = 16.6 Hz), 2.96 (1H, m), 2.20 (1H, m), 1.71–1.33 (6H, m); ^{13}C NMR ($CDCl_3$) δ 171.6, 156.4 (d, J_{CP} = 4.2 Hz), 116.7 (d, J_{CP} = 185 Hz), 61.6 (d, J_{CP} = 7.6 Hz), 57.8, 53.4, 52.3 (d, J_{CP} = 5.6 Hz), 52.2 (d, J_{CP} = 5.6 Hz), 51.7, 32.0 (d, J_{CP} = 2.3 Hz), 25.6, 23.3; ^{31}P NMR ($CDCl_3$) δ 19.3; HRMS (EI, M^+) Calc. for $C_{12}H_{22}O_5NP$: 291.1235. Found 291.1238; and *trans* vinyl phosphonate **14a**. IR (neat, NaCl) 1737 cm^{-1}, ^1H NMR ($CDCl_3$) δ 6.70 (1H, ddd, J_{HH} = 17.3, 8.6 Hz, J_{HP} = 21.7 Hz), 5.67 (1H, dd, J_{HH} = 17.2 Hz, J_{HP} = 20.7 Hz), 3.73 (6H, d, J_{HP} = 11.1 Hz), 3.70 (3H, s), 3.37 (1H, d, J_{HH} = 16.7 Hz), 3.17 (1H, d, J_{HH} = 16.6 Hz), 3.12 (1H, m), 2.94 (1H, m), 2.39 (1H, m), 1.89–1.26 (6H, m); ^{13}C NMR ($CDCl_3$) δ 171.3, 155.2, 117.6 (d, J_{CP} = 188 Hz), 65.1 (d, J_{CP} = 22.7 Hz), 57.2, 53.0, 52.6 (d, J_{CP} = 6.7 Hz), 51.7, 32.6, 25.7, 23.4; ^{31}P NMR ($CDCl_3$) δ 20.8; HRMS (EI, M^+) Calc. for $C_{12}H_{22}O_5NP$: 291.1235. Found 291.1238.

3.22. Synthesis of N-tosyl carbamate derivatives (7)

To a solution of allylic hydroxy phosphonate 2 (1 mmol) in CH_2Cl_2 was added tosyl isocyanate (1.1 mmol) under argon at room temperature. After stirring for 2 h, the mixture was concentrated in vacuo to yield the crude *N*-tosyl carbamate **7**. Yields and physical data are given below.

3.23. Dimethyl [1-(N-tosylcarbamoyloxy)-2-propenyl] phosphonate (**7a**)

Recrystallization from EtOAc/hexanes gave a white solid (72%). IR (neat, NaCl) 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.93 (2H, d, J_{HH} = 8.4 Hz), 7.34 (2H, d, J_{HH} = 8.0 Hz), 5.80 (1H, m), 5.46 (1H, m), 5.35 (2H, m), 3.77 (3H, d, J_{HP} = 10.8 Hz), 3.75 (3H, d, J_{HP} = 10.8 Hz), 2.44 (3H, s); ^{31}P NMR ($CDCl_3$) δ 20.0; HRMS (FAB, MH^+) Calc. for $C_{13}H_{19}NO_7PS$: 364.0620. Found: 364.0622. HRMS (*m*/*z*) in FAB mode Calc. for $C_{13}H_{19}NO_7PS^+$ [$M + H^+$]: 364.0620, found: 364.0622. Anal. Calc. for $C_{13}H_{18}NO_7PS$: C, 42.98; H, 4.99. Found: C, 43.07; H, 5.06%.

3.24. Dimethyl [3-phenyl-1-(N-tosylcarbamoyloxy)-2-propenyl] phosphonate (**7b**)-2-butenyl] phosphonate (**7c**)

Recrystallization white solid (76%). IR (neat, NaCl) 3435, 1754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95 (2H, d, J_{HH} = 8.1 Hz), 7.27 (7H, m), 6.67 (1H, dd, J_{HH} = 15.9 Hz, J_{HP} = 3.8 Hz), 6.13 (1H, m), 5.66 (1H, dd, J_{HH} = 7.8 Hz, J_{HP} = 13.7 Hz), 3.77 (6H, d, J_{HP} = 10.7 Hz), 2.39 (3H, s); ^{13}C ($CDCl_3$) δ 150.5, 144.9, 130.7 (d, J_{CP} = 12.7Hz), 136.2, 135.4, 129.7, 128.9, 128.8, 128.4, 127.1, 118.8 (d, J_{CP} = 3.5 Hz), 71.4 (d, J_{CP} = 174 Hz), 54.5 (d, J_{CP} = 6.8 Hz), 54.3 (d, J_{CP} = 6.7 Hz), 21.8; ^{31}P NMR ($CDCl_3$) δ 19.7; HRMS(FAB, MNa^+) Calc. for $C_{19}H_{22}O_7NPSNa$: 462.0753. Found: 462.0750.

3.25. Dimethyl [1-(N-tosylcarbamoyloxy)-2-butenyl] phosphonate (**7c**)

Recrystallization from EtOAc/hexanes gave a white solid (67%). IR (neat) 1751 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (2H, d, J_{HH} = 8.3 Hz), 7.33 (2H, d, J_{HH} = 8.2 Hz), 5.83 (1H, m), 5.43 (2H, m), 3.77 (3H, d, J_{HP} = 11.4 Hz), 3.74 (3H, d, J_{HP} = 11.0 Hz), 2.44 (3H, s), 1.71 (3H, m); ^{13}C NMR ($CDCl_3$): δ 150.2 (d, $^2J_{CP}$ = 7.5 Hz), 145.2, 136.2, 135.5 (d, J_{CP} = 13.0 Hz), 129.9, 128.7, 121.3, 71.5 (d, $^1J_{CP}$ = 175 Hz), 54.5 (d, $^2J_{CP}$ = 6.9 Hz), 54.3 (d, $^2J_{CP}$ = 6.8 Hz), 22.1, 18.4. ^{31}P NMR ($CDCl_3$): δ 20.0. HRMS (FAB, NBA, MH^+) Calc. for $C_{13}H_{19}NO_7PS$: 378.0776. Found 378.0774. Anal. Calc. for $C_{13}H_{18}NO_7PS$: C, 43.00; H, 4.99. Found: C, 43.07; H, 5.06%.

3.26. Dimethyl [1-(N-tosylcarbamoyloxy)-4-acetoxyl-2-butenyl] phosphonate (**7d**)

Column chromatography [SiO_2, EtOAc:hexanes, 9:1] gave a white solid (70%). ^{1}H NMR ($CDCl_3$) δ 7.93 (2H, d, J_{HH} = 8.4 Hz), 7.35 (2H, d, J_{HH} = 8.1 Hz), 5.83 (2H, m), 5.51 (1H, dd, J_{HH} = 5.9 Hz, J_{HP} = 14.2 Hz), 4.55 (2H, t, J_{HH} = 5.1 Hz), 3.77 (3H, d, J_{HP} = 10.8 Hz), 3.75 (3H, d, J_{HP} = 10.8 Hz), 2.45 (3H, s), 2.07 (3H, s). ^{13}C {^{1}H}NMR ($CDCl_3$): δ 150.0, 145.3, 136.1, 130.0, 128.7, 68.6, 65.0 (d, J_{CP} = 196 Hz), 60.6, 54.7 (d, J_{CP} = 6.9 Hz), 54.6 (d, J_{CP} = 7.5 Hz), 22.0, 21.1. ^{31}P NMR ($CDCl_3$) 20.0. HRMS (FAB, MH^+) Calc. for $C_{16}H_{23}NO_9PS^+$ 436.0831. Found: 436.0840. Anal. Calc. for $C_{16}H_{22}NO_9PS$: C, 44.10; H, 5.09. Found: C, 44.22; H, 5.17%.

3.27. Pd(0)-catalyzed rearrangement of allylic N-tosyl carbamate (**15b–d**)

P(O*i*Pr)$_3$ (133 μL, 0.54 mmol) was added $Pd_2(dba)_3$ (164 mg, 0.18 mmol). The resulting green solution was stirred for 5 min. at room temperature and then a solution of allylic tosyl carbamate **7** (1.60 g, 3.68 mmol) in THF (1 mL) was added. After the reaction was complete (TLC), the reaction mixture was filtered through a pad of celite with Et_2O (500 mL). The solvent was removed in vacuo and the resulting in yellow oil was purified by column chromatography (SiO_2, EtOAc:hexanes, 9:1).

3.28. Dimethyl [(N-tosyl 3-amino)-3-phenyl-1-propenyl] phosphonate (**15b**)

Crytallize with EtOAc (51%). IR (neat, NaCl) 3382 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.66 (2H, d, J_{HH} = 8.3 Hz), 7.25 (5H, m), 7.03 (2H, m), 6.80 (1H, ddd, J_{HH} = 4.8, 17.1 Hz, J_{HP} = 21.8 Hz), 5.88 (1H, ddd, J_{HH} = 1.7, 17.1 Hz, J_{HP} = 18.8 Hz), 5.04 (1H, m), 4.90 (1H, m), 3.70 (3H, d, J_{HP} = 11.1 Hz), 3.69 (3H, d, J_{HP} = 11.1 Hz), 2.42 (3H, s); ^{13}C($CDCl_3$) δ 151.2, 143.8, 137.8, 137.6, 129.8, 129.2, 128.7, 127.4, 127.3, 117.6 (d, J_{CP} = 188 Hz), 59.8 (d, J_{CP} = 22.9 Hz), 52.8, 52.7, 21.7; ^{31}P NMR ($CDCl_3$) δ 20.6; HRMS(FAB, MH^+) Calc. for $C_{18}H_{23}O_5NPS$: 396.1034. Found: 396.1038.

3.29. Dimethyl [N-tosyl 3-amino-1-butenyl] phosphonate (**15c**)

White crystalline solid (67%). ^{1}H NMR ($CDCl_3$): δ 7.74 (2H, d, J_{HH} = 8.3 Hz), 7.28 (2H, d, J_{HH} = 8.1 Hz), 6.60 (1H, ddd, J_{HH} = 5.1, 17.2 Hz, J_{HP} = 22.1 Hz), 5.72 (2H, m), 4.00 (1H, m), 3.65 (3H, d, J_{HP} = 11.1 Hz), 3.65 (3H, d, J_{HP} = 11.1 Hz), 2.41 (3H, s), 1.69 (3H, d, J_{HP} = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 153.6 (d, J_{CP} = 5.4 Hz), 143.6, 138.1, 129.9, 127.2, 115.7 (d, J_{CP} = 188.1 Hz), 54.64 (d, J_{CP} = 5.6 Hz), 52.61 (d, J_{CP} = 23.2 Hz), 21.7, 21.0; ^{31}P NMR ($CDCl_3$) δ 21.7.

3.30. Dimethyl [N-tosyl 3-amino-4-acetoxy-1-butenyl] phosphonate (**15d**)

White crystalline solid (52%) (see Tables 3 & 4). M.p. 123 °C; IR (NaCl neat) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.74 (2H, d, J_{HH} = 8.3 Hz), 7.31 (2H, d, J_{HH} = 8.0 Hz), 6.60 (1H, ddd, J_{HH} = 4.9, 17.2 Hz, J_{HP} = 22.0 Hz), 5.87 (1H, ddd, J_{HH} = 1.7, 17.2 Hz, J_{HP} = 18.7 Hz), 5.64 (1H, d, J_{HH} = 8.3 Hz, NH), 4.24 (1H, m), 4.05 (2H, m), 3.68 (3H, d, J_{HP} = 11.1 Hz), 3.67 (3H, d, J_{HP} = 11.2 Hz), 2.43 (3H, s), 1.94 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.8, 148.3 (d, J_{CP} = 6.3 Hz), 143.9, 137.9, 130.0, 127.2, 119.1 (d, J_{CP} = 189 Hz), 64.9, 54.9 (d, J_{CP} = 22.8 Hz), 52.7 (d, J_{CP} = 5.3 Hz), 52.6, 21.7, 20.7; ^{31}P NMR ($CDCl_3$) δ 20.6; Anal. Calc. for $C_{15}H_{22}NO_7PS$: C, 46.03; H, 5.67. Found: C, 46.35; H, 5.67%.

3.31. General Procedure for Trichloroacetimidate Formation (**16b–c**)

To a stirred solution of hydroxy phosphonates (10 mmol) in dry CH_2Cl_2 at −35 °C was added trichloroacetonitrile (3.01 mL, 30 mmol) and catalytic amount of DBU (0.075 mL, 0.5 mmol). Stirring was continued until reaction was complete (TLC). The solvent was evaporated in vacuo and the residue was purified immediately by column chromatography (SiO_2, CH_2Cl_2:EtOAc).

3.32. Dimethyl (1-trichloroacetimido-3-phenyl-2-propenyl) phosphonate (**16b**)

^{1}H NMR ($CDCl_3$) δ 8.68 (1H, brd s), 7.45–7.42 (2H, m), 7.35–7.31 (3H, m), 6.9 (1H, dd, J_{HH} = 15.9 Hz, J_{HP} = 4.1 Hz), 6.34 (1H, ddd, J_{HH} = 6.8, 15.9 Hz, J_{HP} = 4.9 Hz), 6.13 (1H, dd, J_{HH} = 7.0 Hz, J_{HP} = 14 Hz), 3.9 (3H, d, J_{HP} 10.6 Hz), 3.87 (3H, d, J_{HP} 10.56 Hz); ^{13}C NMR ($CDCl_3$) δ 161.0 (d, J_{CP} = 8.9 Hz), 135.5 (d, J_{CP} = 2.3 Hz), 135.1 (d, J_{CP} = 10.8 Hz), 128.6, 128.5, 126.8, 119.4 (d, J_{CP} = 4.5 Hz), 90.9, 73.6 (d, J_{CP} = 169 Hz), 54.3 (d, J_{CP} = 7.0 Hz), 53.9 (d, J_{CP} = 6.3 Hz); ^{31}P NMR ($CDCl_3$) 19.2.

3.33. Dimethyl (1-trichloroacetimido-2-butenyl) phosphonate (**16c**)

^{1}H NMR ($CDCl_3$) δ 8.48 (1H, brd s), 5.9 (1H, m), 5.73 (1H, dd, J_{HH} = 7.2 Hz, J_{HP} = 12.5 Hz), 5.48 (1H, m), 3.74 (3H, d, J_{HP} = 10.6 Hz), 3.70 (3H, d, J_{HP} = 10.3 Hz), 3.83(3H, s), 1.66 (3H, d, J_{HH} = 4.4 Hz); ^{13}C NMR ($CDCl_3$) δ 160.6 (d, J_{CP} = 12.4 Hz), 132.6 (d, J_{CP} = 12.4 Hz), 120.9 (d, J_{CP} = 3.7 Hz), 73.1

(d, J_{CP} = 169 Hz), 53.7, 54.0 (d, J_{CP} = 6.9 Hz), 53.3 (d, J_{CP} = 6.9 Hz), 17.9; ^{31}P NMR ($CDCl_3$) δ 20.1.

3.34. General procedures for the palladium(II)-catalyzed rearrangement of trichloroacetimidates (**16**)

To a stirred solution of imidate (4.38 mmol) in THF (5 mL) was added palladium chloride benzonitrile complex (168 mg, 0.438 mmol). After the reaction was complete (TLC, or ^{31}P NMR), the solvent was evaporated in vacuo and the crude product was purified by column chromatography (SiO_2, hexane:EtOAc, 1:1) to give the pure 3-trichloroacetamido vinyl phosphonates **18b–c**.

3.35. Dimethyl (3-trichloroacetamido-3-phenyl-1-propenyl) phosphonate (**18b**) [17]

^{1}H NMR ($CDCl_3$) δ 7.45–7.32 (5H, m), 7.01 (1H, ddd, J_{HH} = 17.2, 5.1 Hz, J_{HP} = 22.3 Hz), 5.90 (1H, ddd, J_{HH} = 18.7, 1.6 Hz, J_{HP} = 19.9 Hz), 5.71 (1H, m), 3.76 (3H, d, J_{HP} = 11.1 Hz), 3.74 (3H, d, J_{HP} = 11.1 Hz), ^{13}C NMR ($CDCl_3$) δ 161.3, 149.6 (d, J_{CP} = 6.2 Hz), 137.1 (d, J_{CP} = 3.3 Hz), 129.4, 128.9, 127.4, 117.7 (d, J_{CP} = 187 Hz), 92.5, 57.3 (d, J_{CP} = 22.9 Hz), 52.8 (d, J_{CP} = 6.0 Hz), 52.8 (d, J_{CP} = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 19.8.

3.36. Dimethyl (3-trichloroacetamido-1-butenyl) phosphonate (**18c**) [17]

^{1}H NMR ($CDCl_3$) δ 7.21 (1H, brd d), 6.79 (1H, ddd, J_{HH} = 17.2, 4.9 Hz; J_{HP} = 22.0 Hz), 5.82 (1H, ddd, J_{HH} = 1.6 Hz, J_{HP} = 18.4 Hz), 4.70 (1H, m), 3.76 (3H, d, J_{HP} = 11.0 Hz), 3.73 (3H, d, J_{HP} = 11.1 Hz), 1.45 (3H, d, J_{HH} = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 161.2, 151.7 (d,J_{CP} = 5.4 Hz), 115.9 (d, J_{CP} = 187 Hz), 92.4, 52.5 (d, J_{CP} = 5.9 Hz), 19.4; ^{31}P NMR ($CDCl_3$) δ 20.9.

3.37. Intramolecular aminopalladation and carbonylation to give oxazolidinone (**19**)

A solution of allylic N-tosyl carbamate **6a** (1 mmol), trimethyl orthoformate (18 mmol), and NaOAc (3 mmol) in MeOH (5 mL) was added via syringe to a flask containing $PdCl_2$ (0.1 mmol) and $CuCl_2$ (2.3 mmol) which had been purged with carbon monoxide (via a

Table 3
Crystallographic data for compounds **15d** and **19**

	Vinyl phosphonate **15d**	Oxazolidinine **19**
Empirical formula	$C_{15}H_{22}NO_7PS$	$C_{15}H_{20}NO_9PS$
Formula weight	391.37	421.35
Temperature (K)	140(2)	140(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Orthorhombic
Space group	$P\bar{1}$	$P2_12_12_1$
Unit cell dimensions		
a (Å)	9.7340(7)	9.7620(6)
b (Å)	9.9877(7)	10.3991(7)
c (Å)	10.1982(8)	18.8584(12)
α (°)	91.895(5)	90
β (°)	107.342(5)	90
γ (°)	97.062(6)	90
Volume (Å^3)	936.68(12)	1914.4(2)
Z	2	4
Density (calculated) (Mg m^{-3})	1.388	1.462
Absorption coefficient (mm^{-1})	0.294	0.301
F(0 0 0)	412	880
Crystal size (mm^3)	0.22 × 0.20 × 0.12	0.30 × 0.18 × 0.16
Θ range for data collection (°)	2.06–30.00	2.24–30.10
Index ranges	$-13 \leqslant h \leqslant 12$, $-14 \leqslant k \leqslant 14$, $-14 \leqslant l \leqslant 14$	$-13 \leqslant h \leqslant 13$, $-14 \leqslant k \leqslant 14$, $-26 \leqslant l \leqslant 26$
Reflections collected	22,274	25,360
Independent reflections	5366 [R_{int} = 0.049]	5567 [R_{int} = 0.0649]
Completeness to theta = 30.00° (%)	98.2	99.5
Absorption correction	None	None
Maximum and minimum transmission	0.9656 and 0.9382	0.9535 and 0.9152
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	5366/0/311	5567/0/324
Goodness-of-fit on F^2	1.015	1.021
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0396, wR_2 = 0.0939	R_1 = 0.0423, wR_2 = 0.0892
R indices (all data)	R_1 = 0.0657, wR_2 = 0.1048	R_1 = 0.0681, wR_2 = 0.0977
Absolute structure parameter		0.46(7)
Largest difference peak and hole (e Å^{-3})	0.299 and −0.324	0.390 and −0.320

Table 4
Bond lengths (Å) and angles (°) for **15d**

S(1)–O(7)	1.4329(13)
S(1)–O(6)	1.4356(12)
S(1)–N(1)	1.6197(14)
S(1)–C(9)	1.7612(16)
P(1)–O(3)	1.4715(12)
P(1)–O(2)	1.5714(12)
P(1)–O(1)	1.5718(13)
P(1)–C(1)	1.7724(16)
N(1)–C(3)	1.476(2)
O(1)–C(7)	1.445(2)
O(2)–C(8)	1.450(2)
O(4)–C(5)	1.353(2)
O(4)–C(4)	1.440(2)
O(5)–C(5)	1.198(2)
C(1)–C(2)	1.319(2)
C(2)–C(3)	1.507(2)
C(3)–C(4)	1.517(2)
C(5)–C(6)	1.489(3)
C(9)–C(14)	1.389(2)
C(9)–C(10)	1.396(2)
C(10)–C(11)	1.389(2)
C(11)–C(12)	1.390(3)
C(12)–C(13)	1.393(3)
C(12)–C(15)	1.504(3)
C(13)–C(14)	1.381(3)
O(7)–S(1)–O(6)	119.57(8)
O(7)–S(1)–N(1)	105.66(8)
O(6)–S(1)–N(1)	107.18(7)
O(7)–S(1)–C(9)	108.65(7)
O(6)–S(1)–C(9)	107.24(8)
N(1)–S(1)–C(9)	108.08(7)
O(3)–P(1)–O(2)	109.11(7)
O(3)–P(1)–O(1)	115.36(7)
O(2)–P(1)–O(1)	106.83(7)
O(3)–P(1)–C(1)	114.59(8)
O(2)–P(1)–C(1)	108.56(7)
O(1)–P(1)–C(1)	101.86(7)
C(3)–N(1)–S(1)	120.15(11)
C(7)–O(1)–P(1)	119.92(13)
C(8)–O(2)–P(1)	121.16(12)
C(5)–O(4)–C(4)	115.17(14)
C(2)–C(1)–P(1)	121.10(13)
C(1)–C(2)–C(3)	125.11(15)
N(1)–C(3)–C(2)	112.34(12)
N(1)–C(3)–C(4)	108.54(13)
C(2)–C(3)–C(4)	108.51(13)
O(4)–C(4)–C(3)	108.36(13)
O(5)–C(5)–O(4)	122.20(17)
O(5)–C(5)–C(6)	126.04(18)
O(4)–C(5)–C(6)	111.76(18)
C(14)–C(9)–C(10)	120.92(16)
C(14)–C(9)–S(1)	120.07(13)
C(10)–C(9)–S(1)	118.92(13)
C(11)–C(10)–C(9)	118.58(18)
C(10)–C(11)–C(12)	121.42(18)
C(11)–C(12)–C(13)	118.62(17)
C(11)–C(12)–C(15)	121.3(2)
C(13)–C(12)–C(15)	120.1(2)
C(14)–C(13)–C(12)	121.17(19)
C(13)–C(14)–C(9)	119.28(18)
P(1)–O(5)	1.4588(16)
P(1)–O(6)	1.5646(17)
P(1)–O(7)	1.5657(16)

Table 5
Bond lengths (Å) and angles (°) for **19**

P(1)–C(1)	1.825(2)
S(1)–O(8)	1.4223(18)
S(1)–O(9)	1.4238(18)
S(1)–N(1)	1.6722(17)
S(1)–C(9)	1.749(2)
O(1)–C(8)	1.353(2)
O(1)–C(1)	1.459(3)
O(2)–C(8)	1.196(3)
O(3)–C(4)	1.201(3)
O(4)–C(4)	1.340(3)
O(4)–C(5)	1.445(3)
O(6)–C(6)	1.454(3)
O(7)–C(7)	1.445(3)
N(1)–C(8)	1.384(3)
N(1)–C(2)	1.471(3)
C(1)–C(2)	1.533(3)
C(2)–C(3)	1.530(3)
C(3)–C(4)	1.497(3)
C(9)–C(10)	1.388(3)
C(9)–C(14)	1.389(3)
C(10)–C(11)	1.377(3)
C(11)–C(12)	1.394(4)
C(12)–C(13)	1.382(4)
C(12)–C(15)	1.501(3)
C(13)–C(14)	1.370(4)
O(5)–P(1)–O(6)	114.59(9)
O(5)–P(1)–O(7)	117.15(10)
O(6)–P(1)–O(7)	103.04(10)
O(5)–P(1)–C(1)	113.87(9)
O(6)–P(1)–C(1)	105.86(9)
O(7)–P(1)–C(1)	100.66(9)
O(8)–S(1)–O(9)	121.25(11)
O(8)–S(1)–N(1)	103.85(9)
O(9)–S(1)–N(1)	107.72(10)
O(8)–S(1)–C(9)	109.30(11)
O(9)–S(1)–C(9)	108.72(10)
N(1)–S(1)–C(9)	104.70(9)
C(8)–O(1)–C(1)	109.35(16)
C(4)–O(4)–C(5)	115.6(2)
C(6)–O(6)–P(1)	121.99(18)
C(7)–O(7)–P(1)	119.81(17)
C(8)–N(1)–C(2)	111.97(16)
C(8)–N(1)–S(1)	122.55(15)
C(2)–N(1)–S(1)	124.46(15)
O(1)–C(1)–C(2)	105.00(16)
O(1)–C(1)–P(1)	107.06(14)
C(2)–C(1)–P(1)	116.28(15)
N(1)–C(2)–C(3)	110.36(17)
N(1)–C(2)–C(1)	100.18(17)
C(3)–C(2)–C(1)	112.65(17)
C(4)–C(3)–C(2)	111.37(19)
O(3)–C(4)–O(4)	124.2(2)
O(3)–C(4)–C(3)	125.3(2)
O(4)–C(4)–C(3)	110.5(2)
O(2)–C(8)–O(1)	123.6(2)
O(2)–C(8)–N(1)	127.5(2)
O(1)–C(8)–N(1)	108.88(18)
C(10)–C(9)–C(14)	120.8(2)
C(10)–C(9)–S(1)	120.13(17)
C(14)–C(9)–S(1)	119.05(17)
C(11)–C(10)–C(9)	119.3(2)
C(10)–C(11)–C(12)	120.9(2)
C(13)–C(12)–C(11)	118.1(2)
C(13)–C(12)–C(15)	120.9(2)

Table 5 (*continued*)

C(11)–C(12)–C(15)	120.9(2)
C(14)–C(13)–C(12)	122.3(2)
C(13)–C(14)–C(9)	118.5(2)

balloon). The mixture was stirred at 30–35 °C for 3 days. The mixture was diluted with EtOAc and washed with saturated NH_4Cl, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, EtOAc) to give the oxazolidinone (95%). Recrystallization from Et_2O:hexanes provided a white crystalline solid with crystals suitable for X-ray diffraction studies (see Tables 3–5). ^1H NMR ($CDCl_3$) δ 7.95 (2H, d, J_{HH} = 8.4 Hz), 7.37 (2H, d, J_{HH} = 8.0 Hz), 4.88 (1H, m), 4.68 (1H, dd, J_{HH} = 3.6 Hz, J_{HP} = 1.0 Hz), 3.75 (3H, d, J_{HP} = 10.7 Hz), 3.73 (3H, d, J_{HP} = 10.6 Hz), 3.69 (3H, s), 3.06 (2H, d, J_{HH} = 5.5 Hz), 2.46 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.3, 151.6 (d, J_{CP} = 2.3 Hz), 146.9, 135.2, 130.7, 129.6, 73.3 (d, J_{CP} = 169 Hz), 55.4, 55.14 (d, J_{CP} = 6.8 Hz), 55.09 (d, J_{CP} = 6.9 Hz), 53.2, 39.2 (d, J_{CP} = 10.7 Hz), 22.7; ^{31}P NMR ($CDCl_3$) δ 17.9.

*3.38. Intramolecular aminopalladation and heteroatom elimination to give oxazolidinone (**21**)*

Into a 2-necked flask containing $PdCl_2(CH_3CN)_2$ (0.077 g, 0.3 mmol)under argon was added the solution of allylic *N*-tosyl carbamate **6d** (0.65 g, 1.5 mmol) in THF (3 mL) followed by trimethyl orthoformate (2.9 mL, 27 mmol) and NaOAc (0.37 g, 4.5 mmol). The reaction mixture was heated at reflux for 20 h. The mixture was filtered through a pad of celite with Et_2O (150 mL). The filtrate was concentrated in vacuo and the residue (0.52 g) was purified by column chromatography (1:1 EtOAc to hexanes) gave the oxazolidinone **21** as a yellow oil (45%). ^1H NMR ($CDCl_3$): δ 7.83 (2H, d, J_{HH} = 8.2 Hz), 7.27 (2H, d, J_{HH} = 8.2 Hz), 5.79 (1H, m), 5.46 (1H, d, J_{HH} = 16.9 Hz), 5.34 (1H, d, J_{HH} = 10.1 Hz), 5.02 (1H, ddd, J_{HH} = 3.8, 7.6 Hz, J_{HP} = 15.0 Hz), 4.29 (1H, d, J_{HH} = 3.8 Hz), 3.71 (3H, d, J_{HP} = 10.8 Hz), 3.67 (3H, d, J_{HP} = 10.7 Hz), 2.36 (3H, s); ^{31}P NMR ($CDCl_3$) δ 17.6.

*3.39. Intramolecular aminopalladation and β-hydride elimination to give (**21**)*

A solution of tosyl carbamate **6c** (0.1 g, 0.27 mmol) in THF (5 mL) and DMF (20 drops) was added to flask containing palladium acetate (3.14 mg, 0.014 mmol), copper acetate (0.162 g, 0.81 mmol), and sodium acetate (0.066g, 0.81 mmol). The mixture was stirred at 45 °C for 2 days. The mixture was diluted with EtOAc and washed with saturated NH_4Cl, H_2O, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a mixture of products consisting starting material 47%, oxazolidinone 28%, vinyl phosphonate 20%, hydroxy phosphonate 5%.

4. Supplementary material

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data center, CCDC No. 24385 for compound **15d** and CCDC No. 24386 for compound **19**. Copies of this information may obtained from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1233-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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References

[1] (a) B.J. Rowe, C.D. Spilling, Tetrahedron: Asymmetry 12 (2001) 1701;
(b) M.D. Groaning, B.J. Rowe, C.D. Spilling, Tetrahedron Lett. 39 (1998) 5485;
(c) N.P. Rath, C.D. Spilling, Tetrahedron Lett. 35 (1994) 227;
(d) T. Yokomatsu, T. Yamagishi, S. Shibuya, Tetrahedron: Asymmetry 4 (1993) 1783;
(e) T. Yokomatsu, T. Yamagishi, S. Shibuya, J. Chem. Soc., Perkin Trans. 1 (1997) 1527;
(f) H. Sasai, M. Bougauchi, T. Arai, M. Shibasaki, Tetrahedron Lett. 38 (1997) 2717;
(g) T. Yokomatsu, T. Yamagishi, S. Shibuya, Tetrahedron: Asymmetry 4 (1993) 1779;
(h) T. Arai, M. Bougauchi, H. Sasai, M. Shibasaki, J. Org. Chem. 61 (1996) 2926;
(i) J.P. Duxbury, A. Cawley, M. Thorton-Pett, L. Wantz, J.N.D. Warne, R. Greatrex, D. Brown, T.P. Kee, Tetrahedron Lett. 40 (1999) 4403;
(j) C.V. Ward, M. Jiang, T.P. Kee, Tetrahedron Lett. 41 (2000) 6181.
[2] (a) A. Heisler, C. Rabiller, R. Douillard, N. Goalou, G. Hägele, F. Levayer, Tetrahedron: Asymmetry 4 (1993) 959;

(b) Y.-F. Li, F. Hammerschmidt, Tetrahedron: Asymmetry 4 (1993) 109;
(c) M. Drescher, F.-Y. Li, F. Hammerschmidt, Tetrahedron 51 (1995) 4933;
(d) M. Drescher, F. Hammerschmidt, H. Kahlig, Synthesis (1995) 1267;
(e) G. Eidenhammer, F. Hammerschmidt, Synthesis (1996) 748;
(f) M. Drescher, F. Hammerschmidt, Tetrahedron 53 (1997) 4627;
(g) F. Wuggenig, F. Hammerschmidt, Monatsh. Chem. 129 (1998) 423;
(h) F. Hammerschmidt, F. Wuggenig, Tetrahedron: Asymmetry 10 (1999) 1709.

[3] (a) For reviews of the asymmetric synthesis of hydroxy phosphonates see: D.F. Wiemer, Tetrahedron 53 (1997) 16609;
(b) S.R. Davies, M.C. Mitchell, C.P. Cain, P.G. Devitt, R.J. Taylor, T.P. Kee, J. Organomet. Chem. 550 (1998) 29;
(c) H. Gröger, B. Hammer, Chem. Eur. J. 6 (2000) 943.

[4] (a) For recent reports of the asymmetric synthesis of hydroxy phosphonates see: D. Skropeta, R.R. Schmidt, Tetrahedron: Asymmetry 14 (2003) 265;
(b) O. Pàmies, J.-E. Bäckvall, J. Org. Chem. 68 (2003) 4815;
(c) Y. Zhang, C. Yuan, Z. Li, Tetrahedron 58 (2002) 2973;
(d) M.J. Burk, T.A. Stammers, J.A. Straub, Org. Lett. 1 (1999) 387;
(e) O.I. Kolodiazhnyi, E.V. Griskkun, S. Sheiko, O. Demchuk, H. Thoennessen, P.G. Jones, R. Schmutzler, Tetrahedron: Asymmetry 9 (1998) 1645.

[5] (a) M.A. De la Cruz, H. Shabany, C.D. Spilling, Phosphorus, Sulfur and Silicon 146 (1999) 181;
(b) B. Yan, C.D. Spilling, J. Org. Chem. 69 (2004) 2859;
(c) B.J. Rowe, C.D. Spilling, J. Org. Chem. 68 (2003) 9502;
(d) B.J. Rowe, J. Scholten, C.D. Spilling, Phosphorus, Sulfur and Silicon 177 (2002) 1881;
(e) H. Shabany, C.D. Spilling, Tetrahedron Lett. 39 (1998) 1465.

[6] (a) For examples of β-amino substituted phosphonates see: S.C. Fields, Tetrahedron 55 (1999) 12237;
(b) D.V. Patel, K. Rielly-Gauvin, D.E. Ryono, C.A. Free, W.L. Rogers, S.A. Smith, J.M. DeForrest, R.S. Oehl, E.W. Petrillo Jr., J. Med. Chem. 38 (1995) 4557;
(c) D.V. Patel, K. Rielly-Gauvin, D.E. Ryono, Tetrahedron Lett. 31 (1990) 5587.

[7] (a) For examples of γ-amino substituted phosphonates see: R.G. Hall, Synthesis (1989) 442;
(b) D.M. Walker, J.F. McDonald, J.E. Franz, E.W. Logusch, J. Chem. Soc., Perkin Trans. 1 (1990) 659;
(c) E.W. Logusch, D.M. Walker, J.F. McDonald, J.E. Franz, Plant Physiol. 95 (1991) 1057;
(d) D.M. Walker, J.F. McDonald, E.W. Logusch, Chem. Commun. (1987) 1710;
(e) J.F. Dellaria Jr., R.G. Maki, Tetrahedron Lett. 27 (1986) 2337;
(f) C.Y. McClure, P.K. Mishra, C.W. Grote, J. Org. Chem. 62 (1997) 2437;
(g) T. Hakogi, Y. Monden, S. Iwama, S. Katsumura, Org. Lett. 2 (2000) 2627;
(h) A. Tarnowski, T. Baer, R.R. Schmidt, Bioorg. Med. Cem. Lett. 7 (1997) 573;
(i) T. Hakogi, Y. Monden, M. Taichi, S. Iwama, S. Fujii, K. Ikeda, S. Katsumura, J. Org. Chem. 67 (2002) 4839.

[8] (a) J. Zhu, X. Lu, Tetrahedron Lett. 28 (1987) 1897;
(b) J. Zhu, X. Lu, Chem. Commun. (1987) 1318.

[9] (a) E. Öhler, S. Kanzler, Synthesis (1995) 539;
(b) E. Öhler, S. Kanzler, Phosphorus, Sulfur and Silicon 112 (1996) 71;
(c) M. Attolini, M. Maffei, B. Principato, G. Peiffer, Synlett (1997) 384;
(d) E. Öhler, S. Kanzler, Liebigs Ann. (1997) 1437.

[10] (a) F. Texier-Boullet, A. Foucaud, Synthesis (1982) 165;
(b) P.G. Baraldi, M. Guarneri, F. Moroder, G.P. Pollini, D. Simoni, Synthesis (1982) 653.

[11] (a) J.K. Kozlowski, N.P. Rath, C.D. Spilling, Tetrahedron 51 (1995) 6385;
(b) E. Zymanczyk-Duda, M. Skwarczynski, B. Lejczak, P. Karfarski, Tetrahedron: Asymmetry 7 (1996) 1277.

[12] A. He, B. Yan, A. Thanavaro, C.D. Spilling, N.P. Rath, J. Org. Chem. in press.

[13] V.J. Blazis, K.J. Koeller, C.D. Spilling, J. Org. Chem. 60 (1995) 931.

[14] (a) For earlier non-phosphonate examples see B.M. Trost, J.P. Genet, J. Am. Chem. Soc. 98 (1976) 8516;
(b) B.M. Trost, M.J. Krische, R. Radinov, G. Zanomi, J. Am. Chem. Soc. 118 (1996) 6297.

[15] B. Yan, C.D. Spilling, unpublished results.

[16] (a) S.E. Bystrom, R. Aslanian, J.-E. Backvall, Tetrahedron Lett. 26 (1985) 1749;
(b) R.C. Larock, T.R. Hightower, L.A. Hasvold, K.P. Peterson, J. Org. Chem. 61 (1996) 3584.

[17] E. Ohler, S. Kotzinger, Synthesis (1993) 497.

[18] (a) M. Calter, T.K. Hollis, L.E. Overman, J. Ziller, G.G. Zipp, J. Org. Chem. 62 (1997) 1449, and references cited therein;
(b) L.E. Overman, Ang. Chem. Int., Ed. Engl. 23 (1984) 579;
(c) L.E. Overman, J. Am. Chem. Soc. 98 (1976) 2901;
(d) L.E. Overman, J. Am. Chem. Soc. 96 (1974) 597;
(e) L.E. Overman, Acc. Chem. Res. 13 (1980) 218.

[19] (a) A. Bongini, G. Cardillo, M. Orena, S. Sandri, C. Tomasini, J. Org. Chem. 51 (1986) 4905;
(b) G. CardilloMethods of Organic Chemistry, vol. E21, Thieme Veralag, Stuttgart, 1995, pp. 4746–4759, and references cited therein.

[20] For an example see H. Harayama, A. Abe, T. Sakado, M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, J. Org. Chem. 62 (1997) 2113.

[21] L.S. Hegedus, Transition Metals in the Synthesis of Complex Organic Molecules, second ed., University Science Books, Sausalito, CA, 1999.

[22] (a) For examples see A. Lei, X. Lu, Org. Lett. 2 (2000) 2357;
(b) A. Lei, G. Liu, X. Lu, J. Org. Chem. 67 (2002) 974;
(c) L.E. Overman, T.P. Remarchuk, J. Am. Chem. Soc. 124 (2002) 12;
(d) H. Yokoyama, K. Otaya, H. Kobayashi, M. Miyazawa, S. Yamaguchi, Y. Hirai, Org. Lett. 2 (2000) 2427.