Asymmetric nucleophilic addition to vinylphosphonamidates (Part IV)

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Dedicated to Professor Charles Rees on the occasion of his 75\textsuperscript{th} birthday
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Abstract
Both stereoisomers of 6(R)-methyl-2-propenyl-1,3,2-oxazaphosphorinane-2-oxide 5a and 5b are prepared as single enantiomers. The configurations of the phosphorus atoms in the two compounds are deduced by NMR. The stereoselectivity in the addition of the phenyl carbanion to 5a and 5b are discussed.

Keywords: Vinylphosphonate, oxazaphosphorinane, cuprate, addition, stereoselective

Introduction

\(\beta\)-Substituted phosphonamidates and their phosphonate analogues are useful building blocks for the synthesis of many natural products.\(^1\) We have previously reported that these \(\beta\)-substituted phosphonamidates can be prepared diastereoselectively by the nucleophilic additions to asymmetric vinylphosphonamidates.\(^2,3\) For instance additions of a variety of carbon nucleophiles to chiral racemic 3-diphenylmethyl-2-(prop-2-enyl)-1,3,2-oxazaphosphorinane-2-oxide 1, proceed with good selectivities (typically >80\% de) and the relative configuration of the major diastereomers are \((S_P,SC(\beta))/R_P,RC(\beta))\). Furthermore, the major isomer of these additions can be isolated after one crystallisation as a single diastereomer (Scheme 1).\(^2\)

\[
\text{Scheme 1. RMgBr (6 eq), CuI (6 eq), TMSCl (6 eq), TMEDA (6 eq), -78 °C to -40 °C, Ar.}
\]
We subsequently prepared both phosphorus antipodes of enantiomerically pure vinyl phosphonamidate 2a and 2b, R<sub>p</sub> and S<sub>p</sub> 3-[(R<sub>C</sub>)-1-phenylethyl]-2-(prop-2-enyl)-2-oxo-1,3,2-oxazaphosphorinane; and showed that the additions of carbon nucleophiles to these vinyl phosphonamidates also proceed diastereoselectively (Scheme 2).4

\[ \text{Scheme 2. (a) EtOPCl}_2, \text{Et}_3\text{N, CH}_2\text{Cl}_2, \text{reflux. (b) Allylbromide, reflux, 48 h} ; 30\% \text{ (over two steps). (c) DBU, CH}_2\text{Cl}_2, \text{reflux, 5 days; 89\%. (d) PhMgBr (12 eq), CuI (6 eq), TMSCl (6 eq), TMEDA (6 eq), Et}_2\text{O/THF, -40 °C, 6 h.} \]

Therefore, we have a convenient method for the synthesis of enantiopure -substituted phosphonamidates starting from enantiopure vinyl phosphonamidates 2a and 2b. However, development of alternative enantiopure vinyl phosphonamidates remains a key objective for us. This is because the origin of the chiral induction in the additions to 2a and 2b remains ambiguous since there are two asymmetric centers in the starting vinyl phosphonamidates. Investigation of the asymmetric addition to other vinyl phosphonamidate can help unravel some of the factors that are relevant in the process of these asymmetric inductions and can ultimately be used to further improve diastereoselection in these additions.

Our current model, which successfully predicts the sense of the diastereoselection in the additions to 2a and 2b, suggests that in these compounds the chirality at the phosphorus atom alone is responsible for the chiral induction.2 In other words, the chirality at the carbon atom on the nitrogen side chain has no influence on the chiral induction. To test if the selectivity would be affected if the chiral carbon atom was at a different position. Therefore, we decided to study the additions of carbon nucleophiles to both phosphorus antipodes of enantiomerically pure vinyl phosphonamidate 4a and 4b, R<sub>p</sub> and S<sub>p</sub> 6(R)-methyl-2-propenyl-1,3,2-oxazaphosphorinane-2-oxide.

**Results and Discussion**

Diastereomeric allyl phosphonamidates 4a and 4b were prepared in two steps from N-(phenylmethyl)-1(R)-methylpropanolamine 3,2,4 itself prepared from methyl (R)-3-
hydroxybutyrate in two steps (Scheme 3). The two diastereomers were cleanly separated by chromatography. Unfortunately neither of the materials was crystalline and we were unable to confirm the absolute configuration of the phosphorus atom in these molecules. However, we were able to infer the configuration of the phosphorus atom from NOESY NMR data. In compound 4b, the side chain methylene protons attached to the phosphorus atom show no n.O.e. enhancement with H-6 nor H-4ax. However, in compound 4a, the side chain methylene protons show strong n.O.e. enhancement with H-6 and H-4ax. This would be consistent with the proposed structure for compounds 4a and 4b (Scheme 3).

Both diastereomers were then individually transformed to the corresponding vinyl phosphonamidates 5a and 5b (Scheme 4). Here the NOESY NMR data also confirm our assignment. In compound 5b, the olefinic proton at the position α to the phosphorus atom shows no n.O.e. enhancement with H-6 nor H-4ax. However, in compound 5a, the same proton shows strong n.O.e. enhancement with H-6 and H-4ax.

**Scheme 3.** (a) PhCH$_2$NH$_2$ MeOH, reflux, 5 days; 90%. (b) LiAlH$_4$, THF; 68%. (c) EtOPCl$_2$, Et$_3$N, CH$_2$Cl$_2$, reflux. (d) Allylbromide, reflux, 48 h; 39% (over two steps).

We then carried out the reactions of phenylcuprates in the presence of TMSCl (chlorotrimethylsilane) and TMEDA (N,N,N’,N’-tetramethylethylenediamine) as rate-accelerating additives. The results are outlined below (Scheme 4).

**Scheme 4.** (a) DBU, CH$_2$Cl$_2$, reflux, 5 days; 71%. (b) PhMgBr (6 eq), CuI (6 eq), TMSCl (6 eq), TMEDA (6 eq), Et$_2$O/THF, -40 °C, 6 h.
$^{31}$P NMR analysis of the crude reaction mixture from the addition of the phenyl anion to 5a, which has an S configuration at the phosphorus atom, showed a 5:1 ratio in favour of the higher ppm stereoisomer. That result is consistent with a 10:1 ratio in favour of the higher ppm stereoisomer observed in the addition of the phenyl anion to 2a, which also has an S configuration at the phosphorus atom. Similarly, analysis of the crude reaction mixture from addition of the phenyl anion to 5b, which has an R configuration at the phosphorus atom, showed a 4:1 ratio in favour of the higher ppm stereoisomer. This result is consistent with a 3:1 ratio in favour of the higher ppm stereoisomer observed in the addition of the phenyl anion to 2b, which also has an R configuration at the phosphorus atom. We can conclude that in the addition of the phenyl anion, the sense and magnitude of chiral induction is similar between 2a and 5a and between 2b and 5b.

In conclusion, vinyl phosphonamidates 5a and 5b are useful alternative vinyl phosphonamidate precursors for the synthesis of enantiomerically pure β-substituted phosphoamidates. Furthermore, the similarity in the magnitude and the sense of selectivity in the additions of the phenyl anion suggests that the chiral induction in the additions to 2a or 2b and 5a or 5b, is determined primarily by the chirality at the phosphorus atom as previously proposed (Scheme 5). This confirms our working model which rationalises the observed selectivities based on a combination of steric and internal chelation effects.

![Scheme 5. Diastereofacial selectivity in the additions to 2a and 5a.](image)

**Experimental Section**

**General Procedures.** NMR spectra were obtained in CDCl$_3$ (unless specified) on Bruker AMX360 and AMX400 spectrometers operating respectively at 360 and 400 MHz for $^1$H, 90.6 and 101 MHz for $^{13}$C and 146 and 162 MHz for $^{31}$P. Chemical shifts are reported in ppm. Assignments of NMR spectra are confirmed by COSY, NOSEY, DEPT techniques and C-H correlation spectroscopy where necessary. Mass spectra were obtained on a Jeol AX505W mass spectrometer using electron impact (EI) and chemical ionisation (CI) techniques. Infra-red spectra were recorded on a Perkin-Elmer 1600 FTIR instrument. Chromatography was carried out on silica gel (Merck 9385). Petroleum ether used throughout is boiling point fraction 60-80 °C.
**N-Benzyl-N-[3(R)-hydroxybutyl]amine (3).** A solution of methyl (R)-3-hydroxybutyrate\(^6\) (30.0 g, 0.254 mmol) and benzylamine (27.2 g, 0.254 mmol) in methanol (15 mL) was refluxed for 5 days. The reaction was analysed by nmr to confirm the complete formation of the ester. Solvent was evaporated and the residue was recrystallised from ethylacetate to afford N-benzyl-3(R)-hydroxybutyramide as a white solid (26.7 g first crop, 12.1 g second crop, 5.6 g third crop, 90% total). Mp. 79-80 °C, [\(\alpha\)]\(_D\) = -15.7 ° (c = 0.24, ethanol); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.21 (3H, d, J = 7 Hz, CH\(_3\)CH), 2.28 (1H, dd, J = 10 Hz, 17 Hz, CHHH), 2.37 (1H, dd, J = 3Hz, 17 Hz, CHH), 3.89 (1H, bs, OH), 4.18 (1H, m, MeCHO), 4.42 (2H, d, J = 6 Hz, CH\(_2\)N), 6.42 (1H, bs, NH), 7.27-7.35 (5H, m, aromatic H). \(^1^C\) NMR (CDCl\(_3\)): \(\delta\) 22.87 (CH\(_3\)), 43.37 (CH\(_2\)CO), 43.86 (CH\(_2\)Ph), 64.86 (MeCHO), 127.55 (aromatic CH), 127.72 (2 x aromatic CH), 128.74 (2 x aromatic CH), 137.97 (aromatic C), 172.28 (CO); m/z (CI, ammonia) 387 (M\(^2\)H\(^+\), 45), 211 (MNH\(_4^+\), 61), 194 (MH\(^+\), 100); HRMS calc for C\(_{11}\)H\(_{16}\)NO\(_2\) (MH\(^+\)) 194.1181, found 194.1151. N-Benzyl-3(R)-hydroxybutyramide (24.18 g, 0.125 mmol) was added to a cooled suspension of lithium aluminium hydride (10 g, 0.263 mmol) in THF (250 mL) over 30 minutes. The mixture was refluxed for 3 hours and then quenched by sequential slow addition of water (10 mL), 15% aqueous sodium hydroxide (10 mL) and water (27 mL). Solid was filtered off and the filtrate was stripped of solvent in vacuo to afford the title compound as a pale yellow oil (15.31 g, 68%). [\(\alpha\)]\(_D\) = + 1.8 ° (c = 0.5, ethanol); \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.17 (3H, d, J = 6 Hz, CH\(_3\)CH), 1.51-1.62 (2H, m, CCH\(_2\)C), 2.78 (1H, ddd, J = 4.5 Hz, 9.5 Hz, 11Hz, CHHNN), 3.00 (1H, ddd, J = 4 Hz, 4.5 Hz, 22 Hz, CHHN), 3.74 (1H, d, J = 13 Hz, CHPH), 3.82 (1H, d, J = 13 Hz, CHPhH), 3.98 (1H, m, MeCHO), 7.23-7.28 (5H, m, aromatic H). \(^1^C\)\({H}\) NMR (CDCl\(_3\)): \(\delta\) 23.51 (CH\(_3\)), 36.7 (CCH\(_2\)C), 48.20 (NCH\(_2\)), 53.77 (CH\(_2\)Ph), 69.54 (MeCHO), 127.17 (aromatic CH), 128.15 (2 x aromatic CH), 128.48 (2 x aromatic CH), 139.38 (aromatic C); m/z (CI, ammonia) 359 (M\(^2\)H\(^+\), 20), 180 (MH\(^+\), 100); HRMS calc for C\(_{11}\)H\(_{18}\)NO (MH\(^+\)) 180.1388, found 180.1360.

(6R,2R) 6-Methyl-3-benzyl-2-(prop-2′-enyl)-1,3,2-oxazaphosphorinane-2-oxide (4a) and (6R,2S) 6-Methyl-3-benzyl-2-(prop-2′-enyl)-1,3,2-oxazaphosphorinane-2-oxide (4b).

Triethylamine (6.80 mL, 49.0 mmol) was added to a refluxing solution of ethyldichlorophosphite (3.608 g, 24.5 mmol) in DCM (50 mL) maintained under a nitrogen atmosphere. The solution was stirred for 10 minutes before addition of N-Benzyl-N-[3(R)-hydroxybutyl]amine (4.395 g, 24.5 mmol) as a solution in DCM (20 mL). The stirring was continued overnight. The solvent was evaporated, diethylether (50 mL) was added and the mixture was filtered through celite under a blanket of nitrogen gas. The filtrate was evaporated to afford 2-ethoxy-6-methyl-3-benzyl-1,3,2-oxazaphosphorinane as a sticky oil. This was dissolved in a large excess of allyl bromide (21.5 mL) and refluxed under an argon atmosphere for 1.5 days. Evaporation of solvent followed by chromatography using ethyl acetate as eluent afforded (6R,2R) 6-Methyl-3-benzyl-2-(prop-2′-enyl)-1,3,2-oxazaphosphorinane-2-oxide as an oil (1.52 g, 23%). R\(_f\) 0.25 (ethyl acetate). \(^1^H\) NMR (CDCl\(_3\)): \(\delta\) 1.36 (3H, dd, J\(_H\) = 7 Hz, J\(_P\) = 2 Hz, CH\(_3\)H), 1.64-1.78 (2H, m, CH\(_2\) CH\(_2\)CH\(_2\)H), 2.76 (2H, ddd, J\(_H\) = 1.7 Hz, J\(_P\) = 19 Hz, PCH\(_2\)H), 2.92-3.12 (2H, m, CH\(_2\)N), 3.85 (1H, dd, J\(_H\) = 15 Hz, J\(_P\) = 7 Hz, PhCHH), 4.42 (1H, m, CH\(_3\)MeO), 4.48 (1H, dd, J\(_H\) = 15 Hz, J\(_P\) = 7 Hz, PhCHH), 5.13-5.26 (2H, m, CH\(_2\)=), 5.90 (m, CH=), 7.21-7.58 (5H, m, aromatic H). \(^3^P\)\{H\} NMR (CDCl\(_3\)):
\[ \delta 24.62. \quad ^{13}\text{C}\{\text{H}\} \text{ NMR (CDCl}_3\}: \delta 22.97 (d, J_P = 7 Hz, Me), 31.16 (d, J_P = 119 Hz, PCH\_2), 33.88 (d, J_P = 5 Hz, C\_5), 45.27 (d, J_P = 2 Hz, CH\_2N), 51.72 (d, J_P = 4 Hz, CH\_2Ph), 76.87 (d, J_P = 7 Hz, CHMeO), 118.81 (d, J_P = 13 Hz, CH\_2\_=), 127.83 (aromatic CH), 128.8 (2 x aromatic CH), 129.05 (d, J_P = 10 Hz, -CH\_=), 138.12 (d, J_P = 5 Hz, aromatic C) ; m/z (CI, ammonia) 283 (M\_NH\_4^+ + 61), 266 (MH\_+, 14), 254 (100); HRMS calc for C\_14H\_20NO\_2P (MH\_+) 266.1310, found 266.1303.

Further elution of the chromatography column with a gradient of 2-5% v/v methanol in ethylacetate afforded (6R,2S) 6-Methyl-3-benzyl-2-(prop-2\_′-eny)-1,3,2-oxazaphosphorinane-2-oxide as an oil (1.05 g, 16%). R\_f 0.05 (ethyl acetate).

\[ \delta 1.32 (3H, dd, J_H = 6 Hz, J_P = 1 Hz, CH\_3-C\_6), 1.71-1.79 (2H, m, CH\_2 CH\_2CH\_2), 1.95 (3H, dd, J_H = 2 Hz, J_P = 4 Hz, CH\_3CH\_=), 2.85-3.13 (2H, m, CH\_2N), 3.89 (1H, dd, J_H = 15 Hz, J_P = 4 Hz, PhCH\_2), 4.23 (1H, dd, J_H = 15 Hz, J_P = 10 Hz, PhCH\_2), 4.65 (1H, m, CHMeO), 5.73 (1H, ddd, J_H = 2.17 Hz, J_P = 19 Hz, MeCH\_=), 6.90 (1H, ddd, J_H = 7.17 Hz, J_P = 21 Hz, PCH\_=), 7.24-7.37 (5H, m, aromatic H). \quad ^{31}\text{P}\{\text{H}\} \text{ NMR (CDCl}_3\}: \delta 20.70. \quad ^{13}\text{C}\{\text{H}\} \text{ NMR (CDCl}_3\): \delta 20.08 (d, J_P = 23 Hz, CH\_3CH\_=), 22.39 (d, J_P = 9 Hz, CH\_3-C\_6), 33.26 (d, J_P = 3 Hz, C\_5), 44.42 (CH\_2N), 51.22 (d, J_P = 5 Hz, CH\_2Ph), 72.64 (d, J_P = 6 Hz, CHMeO), 121.17 (d, J_P = 180 Hz, PCH\_=), 127.37 (aromatic CH), 128.13 (aromatic CH), 128.48 (aromatic CH), 137.63 (d, J_P = 8 Hz, aromatic C), 150.25 (d, J_P = 5 Hz, MeCH\_=); m/z (EI) 266 (MH\_+, 54), 225 (12), 175 (100); HRMS calc for C\_14H\_20NO\_2P (MH\_+) 266.1310, found 266.1259.

(6R,2S, 2\′S) 6-Methyl-3-benzyl-2-(2\′-phenylpropyl)-1,3,2-oxazaphosphorinane-2-oxide (6b).

Phenyl magnesium bromide (3M solution in diethylether, 3.0 mL, 9.00 mmol) was added to a stirred suspension of Cul (0.86 g, 4.53 mmol) in dry diethyl ether (7.8 mL), maintained under a dry argon atmosphere at –40 °C. After 45 minutes, the solution was cooled to –78 °C and TMSCl (0.57 mL, 4.53 mmol) was added followed after 10 min. by TMEDA (0.68 mL, 4.53 mmol) and then a solution of (6R,2S) 6-Methyl-3-benzyl-2-(prop-1\′-eny)-1,3,2-oxazaphosphorinane-2-oxide 5b (0.20 g, 0.075 mmol) in dry THF (7.8 ml). Reaction was monitored by tlc (EtO\Ac as eluant) and was found to be complete after 5 hours. The reaction mixture was quenched by
addition of sat. aqueous NH₄Cl (50 mL) and filtered through Celite®. Solid was washed with ethylacetate (50 mL). The organic and aqueous phases of the filtrate were separated and the aqueous phase was washed with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine and then dried over MgSO₄. Evaporation of solvent afforded a green oil. The crude product was directly chromatographed on silica gel (Merck 9385) using EtOAc as eluent to afford the title compound as an oil (180 mg, 69%). A fraction containing unreacted starting material was also isolated (20 mg). ¹H NMR (CDCl₃): δ 1.20 (3H, dd, J H = 7 Hz, J P = 1 Hz, CH₃CHPh), 1.37 (3H, d, J H = 6 Hz, CH₂-C6), 1.54-1.79 (2H, m, CH₂ CH₃CH₂), 2.14 (2H, m, CH₃P), 2.68-3.02 (1H, m, CHHN) 3.17-3.32 (2H, m, CHHN and MeCHPh), 3.71 (1H, dd, J H = 15 Hz, J P = 9 Hz, PhCHH), 4.03 (1H, dd, J H = 15 Hz, J P = 6 Hz, PhCHH), 4.46 (1H, m, CHMeO), 7.17-7.31 (10H, m, aromatic H). ³¹P{H} NMR (CDCl₃): δ 31.60. ¹³C{H} NMR (CDCl₃): δ 22.08 (d, J P = 8 Hz, CH₃CHPh), 24.41 (d, J P = 10 Hz, CH₃-C6), 32.84 (d, J P = 3 Hz, C-5), 35.31 (d, J P = 3 Hz, MeCHPh), 37.26 (d, J P = 131 Hz, CH₂P), 44.20 (CH₂N), 51.22 (d, J P = 4 Hz, CH₂Ph), 72.45 (d, J P = 7 Hz, CHMeO), 126.28 (aromatic CH), 126.78 (aromatic CH), 127.36 (aromatic CH), 128.25 (aromatic CH), 128.47 (aromatic CH), 128.52 (aromatic CH), 137.66 (d, J P = 5 Hz, aromatic C), 147.10 (d, J P = 10 Hz, aromatic C); m/z (EI) 343 (MH⁺, 14), 252 (100), 225 (90); HRMS calc for C₂₀H₂₆NO₂P (MH⁺) 343.1701, found 343.1664.

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References