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Stereocontrolled synthesis of 3-amino-2-hydroxyalkyl diphenylphosphine oxides mediated by chiral azetidinium salts and epoxyamines

Bożena Krawiecka and Agata Jeziorna*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland

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Abstract—The stereocontrolled synthesis of amino hydroxyalkyl diphenylphosphine oxides has been achieved starting from (2*S*,3*S*)-*N*,*N*-dibenzyl-3-hydroxy-2-methylazetidinium bromide or (1*R*),[1′(*S*)-(dibenzylamino)ethyl]oxirane. The regioselective ring opening of both heterocyclic systems at the less substituted carbon atom with phosphorus nucleophiles proceeded with full stereochemical integrity.

1. Introduction

Enantiomerically pure phosphorus compounds are in great demand as chiral auxiliaries for asymmetric synthesis.[1] For many of these compounds, chirality resides not in phosphorus but rather in the carbon skeleton.[2,3c]

Chiral phosphines constitute the main family of ligands for catalysis.[3] During the last ten years, much attention has been paid to chiral aminophosphine ligands or generally to functionalized phosphines.[3b,c]

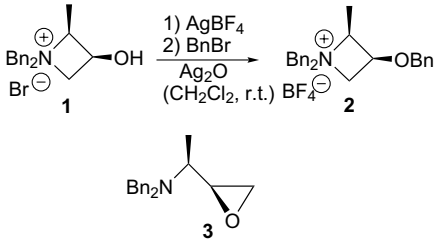
Our laboratory has been engaged in the study of the ring opening reactions of 3-hydroxyazetidinium salts and amino oxiranes with phosphorus-containing nucleophiles which lead to β-hydroxy-γ-aminoalkylphosphonates and the corresponding phosphine oxides on a propane and/or butane skeleton.[4]

Recently, Spanish authors[5,6] demonstrated that 3-hydroxyazetidinium salts and amino oxiranes could be prepared in over 98% enantiomerically pure form from natural amino acids. This finding opened the possibility to prepare a variety of interesting compounds in a stereocontrolled manner, using our strategy. In this letter we describe the preliminary results of our studies on the stereocontrolled synthesis of 3-amino-2-hydroxyalkyl diphenylphosphine oxides.

2. Results and discussion

The starting dibenzyl protected azetidinium salt **1** as well as oxirane **3** were prepared according to the procedure described by Barluenga et al.[5] and Concellón et al.[6] from L-alanine. The spectroscopic and optical properties of **3** were in accord with those described in the literature.[5,6] (2*S*,3*S*)-*N*,*N*-Dibenzyl-3-hydroxy-2-methylazetidinium bromide **1** has been fully characterized spectroscopically.[7]

From our previous studies[4] it was clear that for the reaction of **1** with phosphorus nucleophiles the hydroxyl should be protected to avoid side reactions. The procedure for the protection of the –OH group in the



Scheme 1.

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* Corresponding author. Tel.: +48 (42)6803217; fax: +48 (42)6847126; e-mail: agabak@bilbo.cbmm.lodz.pl

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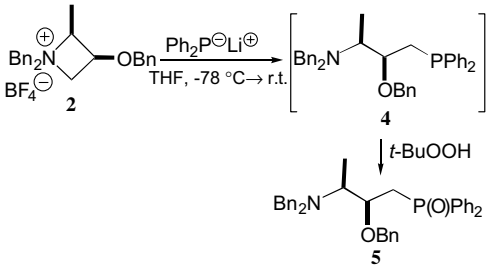
azetidinium salt used previously[4b] required rather drastic reaction conditions. For the chiral salt **1** we decided to elaborate a possibly milder procedure. However, several typical methods for benzylation or silylation of the –OH group failed. The best result was achieved using the reaction with benzyl bromide in the presence of Ag_2O and molecular sieves 4 Å (24 h, room temperature, CH_2Cl_2).[8] This process required the change of counter-anion, thus bromide was first exchanged for BF_4^- (with $AgBF_4$) (Scheme 1). The resultant product was purified by column chromatography and fully characterized spectroscopically.[9]

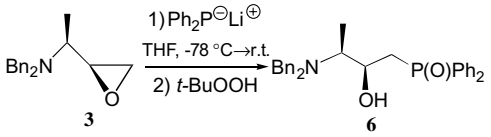
The azetidinium salt **2** was subjected to reaction with lithium diphenyl phosphide (1.5 equiv) in THF, at −78 °C, for 12 h. Separately prepared lithium diphenylphosphide was added into the THF solution of the azetidinium salt at low temperature, under argon. The reaction course was followed by ^{31}P NMR spectroscopy which showed that the appearance of the phosphine **4** and the disappearance of the phosphorus substrate was rather slow. When the reaction was quenched the unchanged substrate was still present in the reaction mixture. Phosphine **4** was oxidized with *tert*-butyl peroxide and phosphine oxide **5** was isolated and purified by column chromatography (yield: 40%).[10] The yield was not optimized (Scheme 2).

The amino hydroxy phosphine oxide **6** with the same stereochemistry but bearing a free hydroxy function was obtained from oxirane **3** by reaction with the same anion, followed by oxidation (Scheme 3). The reaction with oxirane **3** was carried out without the addition of $BF_3{\cdot}Et_2O$ typically used in other similar reactions.[4c] Its absence decreases the reaction rate and as a consequence **6** was isolated in 40% yield,[11] which is consistent with the results observed for **5**.

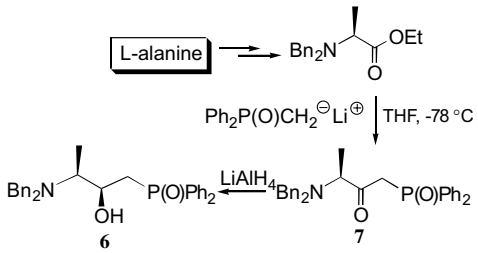
The phosphine oxides, obtained from both starting materials, **2** and **3**, are formed as a result of regioselective ring opening of both heterocyclic systems at the less



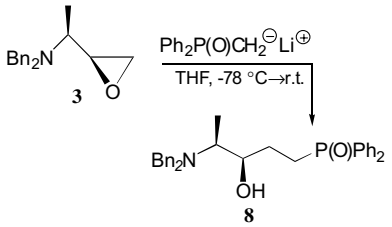
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

substituted carbon atom. Thus, the full stereochemical integrity of the starting materials is retained in the reaction products.

^{31}P NMR spectroscopy showed in each case only one signal for one diastereoisomer and ^{1}H and ^{13}C NMR spectra were in accord with the structures of the products.

The enantiomeric purity of the 3-amino-2-hydroxyalkyl phosphine oxides was additionally confirmed by esterification of the hydroxy group with (*R*)-(−)-α-methoxyphenylacetic acid, using the described procedure.[12] Only one signal for one diastereoisomer was visible in the ^{31}P NMR spectra.

For comparison, an alternative known approach[13] was applied to prepare **6**. The synthesis involved the reaction of the carbanion generated from methyldiphenylphosphine oxide with the ethyl ester of *N*,*N*-dibenzyl protected alanine, followed by reduction of ketophosphine oxide **7** (yield: 87%)[14] with $LiAlH_4$ (yield: 66%) (Scheme 4). The phosphine oxide **6** prepared according to Scheme 4 exhibited the same spectral and optical properties as that obtained from oxirane **3**.

Using the carbanion generated from methyldiphenylphosphine oxide in a reaction with oxirane **3** we obtained a phosphine oxide possessing a five carbon skeleton (Scheme 5). The ^{31}P, ^{1}H, and ^{13}C NMR spectra of **8** were in agreement with the assigned structure.[15]

3. Conclusion

In summary, we have developed a stereocontrolled synthesis of 3-amino-2-hydroxyalkyl(diphenyl)phosphine oxides starting from (2*S*,3*S*)-*N*,*N*-dibenzyl-3-benzyloxy-2-methylazetidinium tetrafluoroborate or

from (1*R*),[1′(*S*)-(dibenzylamino)ethyl] oxirane and lithium phosphide or the carbanion generated from methyl-(diphenyl)phosphine oxide. Regioselective opening of the azetidinium and oxirane rings at the less substituted carbon atom with the nucleophile enables a ready access to possible precursors of tridentate ligands or building blocks of the determined configuration and optical purity.

Acknowledgements

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9. (2*S*,3*S*)-1,1-Dibenzyl-3-benzyloxy-2-methylazetidinium tetrafluoroborate **2**. Purification: column chromatography, eluent CH_2Cl_2–MeOH (30:1), $R_f = 0.58$. Yield: 68%, $[\alpha]_D^{20}$ +18.1 (*c* 1.2, CH_2Cl_2). IR(KBr): ν_{max}(neat)/cm^{-1}: 3434 w br, 3041 w, 2927 w, 2869 w, 1498 m, 1454 m, 1355 m, 1172 m, 1142 m, 1071 s, 1048 s, 1036 s, 754 m, 704 m, 520 w. ^{1}H NMR (500.13 MHz, CD_3OD): $\delta_H = 1.53$ (d, $J = 7.0$, 3H, CH_3CH), 4.04–4.07 (m, 1H, CH_3CH), 4.15 and 4.50 (AB, $J_{AB} = 13.4$, 2H, $N(CH_2Ph)$), δ_A: 4.17 and δ_B: 4.29 (ABX, $J_{A-B} = 12.2$, $J_{A-X} = 3.0$, $J_{B-X} = 5.9$, 2H, $>NCH^AH^B_{(ring)}$), 4.49 and 4.94 (AB, $J_{AB} = 13.2$, 2H, NCH_2Ph), 4.56 (d, $J = 4.6$, 2H, OCH_2Ph), 5.09 (quintet, $J = 6.9$, 1H, CHOBn), 7.29–7.57 (15H, $CH_{(aromatic)}$). ^{13}C NMR (125.76 MHz, CD_3OD): $\delta_C = 8.87$ (CH_3), 61.43 and 63.54 (NCH_2Ph), 64.24 ($>NCH_{2(ring)}$), 71.37 ($CH(CH_3)$), 73.68 (OCH_2Ph), 75.95 (CHOBn), 127.9, 129.37, 129.77, 130.52, 130.59, 130.66, 131.55, 131.85 ($C_{(aromatic)}$), 133.65, 133.71, 138.29 ($C_{(aromatic\ ipso)}$). MS (FAB): 358.2 $(M-BF_4)^+$ (100%). HRMS(FAB) $(M-BF_4)^+$: $C_{25}H_{28}NO$. Calcd 358.2171. Found: 358.2165.
10. (1*S*,2*S*)-*N*,*N*-Dibenzyl-(*N*-1-methyl-2-benzyloxy-3-diphenylphosphinoyl)amine **5**. Purification: column chromatography, eluent CH_2Cl_2–MeOH (30:1), $R_f = 0.33$. Yield: 40%. $[\alpha]_D^{20}$ −38.2 (*c* 1.4, MeOH). IR(film): ν_{max}(neat)/cm^{-1}: 3437 m br, 3059 s, 3027 s, 2978 m, 2963 m, 2931 m, 2912 m, 2875 m, 2833 m, 2804 m, 1960 w, 1890 w, 1737 m, 1643 w, 1494 s, 1453 s, 1437 s, 1362 m, 1243 m, 1188 s, 1117 s, 1069 s, 1027 s, 998 m, 956 m, 910 w, 812 m, 747 s, 697 s, 538 w. ^{31}P NMR (81.03 MHz, $CDCl_3$): 30.89. ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta_H = 1.12$ (d, $J = 6.8$, 3H, CH_3CH), δ_A: 2.54 and δ_B: 2.84 (dABX, $J_{A-B} = 15.8$, $J_{A-X} = 11.0$, $J_{A-P} = 3.1$, $J_{B-X} \approx J_{B-P} = 8.1$, $2 \times 2H$, CH_2P), 2.63 (td, $J = 6.7$; 3.3, 1H, CH_3CH), 3.31 and 4.07 (AB, $J_{AB} = 13.5$, 2H, CH_2Ph), 3.85–3.90 (m, 1H, CHOBn), 4.35 and 4.58 (AB, $J_{AB} = 11.7$, 2H, OCH_2Ph), 7.00–7.74 (m, 25 H, ($CH_{(aromatic)}$)). ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta_C = 9.89$ (CH_3), 34.64 (d, $J_{C-P} = 71.8$, CH_2P), 55.67 (NCH_2Ph), 57.80 (d, $J_{C-P} = 9.5$, $CHCH_3$), 73.26 (OCH_2Ph), 79.34 (d, $J_{C-P} = 1.8$ $CHOCH_2Ph$), 127.15, 127.22, 127.63, 128.17, 128.52, 128.65, 128.75, 128.77, 128.86, 129.51, 130.74, 130.82, 131.10, 131.64, 131.45 ($C_{(aromatic)}$), 138.87, 141.10 ($C_{(aromatic\ ipso)}$). MS (FAB): 560.4 $(M+H)^+$ (35%). HRMS(FAB) $(M+Na)^+$: $C_{37}H_{38}NPO_2$+Na Calcd 582.2538. Found: 582.2546.
11. (2*S*,3*S*)-2-Dibenzylamino-4-diphenylphosphinoyl-butan-3-ol, **6** Purification: column chromatography, eluent CH_2Cl_2–MeOH (20:1), $R_f = 0.27$. Yield: 40%. $[\alpha]_D^{20}$ −23.1 (*c* 1.4, MeOH). IR(film): ν_{max}(neat)/cm^{-1}: 3331 m br, 3058 m, 2806 m, 1493 m, 1454 m, 1437 s, 1176 s, 1119 s, 1070 m, 1027 m, 997 m, 793 s, 750 vs, 697 vs, 506 m. ^{31}P NMR (81.03 MHz, $CDCl_3$): 32.77. ^{1}H NMR (200.13 MHz, $CDCl_3$): $\delta_H = 1.09$ (d, $J = 6.72$, 3H, CH_3CH), 2.08–2.71 (m, 2H+1H, CH_2P, CH_3CH), 3.31 and 3.86 (AB, $J_{AB} = 13.4$, 4H, CH_2Ph), 3.95–4.05 (m, 1H, CHOH), 4.43 (br s, 1H, OH) 7.15–7.81 (m, 20 H, ($CH_{(aromatic)}$)). ^{13}C NMR (50.29 MHz, $CDCl_3$): $\delta_C = 8.43$ (CH_3), 34.49 (d, $J_{C-P} = 72.5$, CH_2P), 53.80 (NCH_2Ph), 58.90 (d, $J_{C-P} = 13.58$, $CHCH_3$), 67.48 (CHOH), 127.07, 128.33, 128.49, 128.59, 129.05, 130.64, 130.83, 131.03, 131.55, 139.14 ($C_{(aromatic)}$). MS (FAB): 470.4 $(M+H)^+$ (100%). HRMS(FAB) $(M+H)^+$: $C_{30}H_{33}NPO_2$ Calcd 470.2249. Found: 470.2231.
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14. (2*S*)-2-*N*,*N*-Dibenzylamino-3-diphenylphosphinoyl-butan-3-one, **7**. Purification: column chromatography, eluent CH_2Cl_2–MeOH (15:1), $R_f = 0.43$. Yield: 90%. $[\alpha]_D^{20}$ −48.8 (*c* 2.1, MeOH). IR(Nujol): ν_{max}(neat)/cm^{-1}: 3023 w, 2806 w, 1709 s (C=O), 1483 w, 1456 w, 1438 m, 1376 m, 1203 s, 1189 s, 1142 m, 1124 s, 1076 m, 1029 m, 867 w, 799 w, 754 s, 722 s, 698 s, 559 w, 528 m. ^{31}P NMR (81.03 MHz, $CDCl_3$): 25.75. ^{1}H NMR (200.13 MHz, $CDCl_3$): $\delta_H = 0.99$ (d, $J = 6.6$, 3H, CH_3CH), 3.66 (q, $J = 6.7$, 1H, CH_3CH), 3.39 and 3.64 (AB, $J_{AB} = 13.5$, $2 \times 2H$, CH_2Ph), 3.44–3.55 (m, 1H, CH^AH^BP), 4.20 (dd, $J = 13.8$; 15.2, 1H, CH^AH^BP), 7.24–7.67 (m, 20 H, ($CH_{(aromatic)}$). ^{13}C NMR (50.29 MHz, $CDCl_3$): $\delta_C = 6.20$ (CH_3), 42.36 (d, $J_{C-P} = 59.9$, CH_2P), 54.64 (CH_2Ph), 63.63 ($CHCH_3$), 127.31, 128.29, 128.36, 128.46, 128.59, 128.96, 130.95, 131.11, 131.86, 138.87 ($C_{(aromatic)}$), 203.83 (C=O). MS (FAB): 478.3 $(M+H)^+$ (96%). HRMS(FAB) $(M+H)^+$: $C_{30}H_{31}NPO_2$ Calcd 468.2092. Found: 468.2102.

15. (2*S*,3*S*)-2-Dibenzylamino-5-diphenylphosphinoyl-pentan-3-ol **8**. Purification: column chromatography, eluent CH_2Cl_2–MeOH (20:1), $R_f = 0.31$. Yield: 42%. $[\alpha]_D^{20}$ −3.9 (*c* 2.1, MeOH). IR(film): ν_{max}(neat)/cm^{-1}: 3060 w, 3028 w, 2961 m, 2930 m, 2499 br m, 2064 w, 1494 w, 1438 s, 1379 w, 1177 s, 1122 s, 1073 w, 980 m, 749 s, 699 s, 513 w. ^{31}P NMR (81.03 MHz, $CDCl_3$): 33.84. ^{1}H NMR (200.13 MHz, CD_3OD): $\delta_H = 0.99$ (d, $J = 7.45$, 3H, CH_3CH), 2.21–2.56 (m, 4H, CH_2CH_2P) 2.30 and 3.79 (AB, $J_{AB} = 13.2$, 2 × 2H, CH_2Ph), 3.46–3.58 (m, 2H, C*H*OH, CH_3C*H*), 7.17–7.76 (m, 20 H, $CH_{(aromatic)}$). ^{13}C NMR (50.29 MHz, $CDCl_3$): $\delta_C = 7.93$ (*C*H_3), 25.27 (d, $J_{C-P} = 73.20$, *C*H_2P), 25.14 (*C*H_2CH_2P), 54.15 (N*C*H_2Ph), 57.62 (*C*HCH_3), 70.62 (d, $J_{C-P} = 13.6$, *C*HOH), 127.16, 128.39, 128.60, 128.93, 130.48, 130.58, 130.67, 130.76, 131.56 ($C_{(aromatic)}$), 138.65 ($C_{(aromatic\ ipso)}$). MS (FAB): 484.3 $(M+H)^+$ (63%).