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Enantioselective desymmetrization of phospholene *meso*-epoxide by nucleophilic opening of the epoxide

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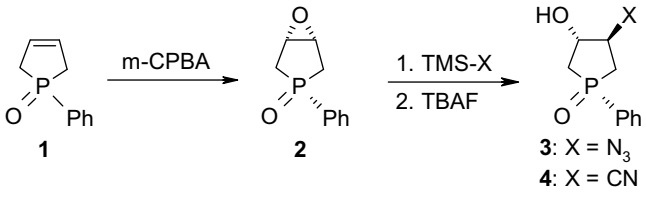
Abstract—A convenient synthesis of enantioenriched P-stereogenic *trans*-3-hydroxy-4-azido- and *trans*-3-hydroxy-4-cyanophospholane oxides has been achieved by ring opening of 3,4-epoxy-1-phenylphospholane-1-oxide using trimethylsilyl azide and trimethylsilyl cyanide in the presence of salen–Al complex. The enantioselectivity of the studied asymmetric ring-opening reactions reached 72% in the best case.

The asymmetric ring opening of *meso*-epoxides catalyzed by chiral metal complexes has emerged as one of the most useful methodologies in the field of asymmetric synthesis. In the last two decades, a number of successful strategies based on this transformation have been developed for targeted synthesis of cyclic and acyclic enantiopure compounds containing carbon stereogenic centres.[1]

In the course of our research programme directed towards the synthesis of P-stereogenic phosphine derivatives[2–4] we aimed to approach the synthesis of functionalized nonracemic five-membered ring monophosphines starting from a readily available achiral 3,4-epoxy-1-phenylphospholane-1-oxide **2**.[5] Epoxyphospholane **2** can be obtained on a large scale from 1-phenyl-3-phospholene-1-oxide **1**[6] by treatment with *m*-chloroperbenzoic acid in refluxing chloroform as described by Arbuzov et al.[7] and by Symmes and Quin[8] who demonstrated also that the peracid oxidation of 3-phospholene oxides were face-selective and provided a single epoxide stereoisomer (Scheme 1). Recently, we described the use of epoxyphospholane **2** in the enantioselective rearrangements leading to the formation of a phosphorus stereogenic centre within the framework of a five-membered ring containing an endocyclic allylic alcohol functionality in its structure.[3] In this communication we present our study on the asymmetric opening of the epoxide **2** by azide and cyanide nucleophiles in the presence of chiral Lewis acid catalyst (Scheme 1). Both target products could find use as intermediates for the synthesis of phosphasugar derivatives.[9,10]



Scheme 1. Only relative configurations of **3** and **4** are depicted.

Quite unexpectedly, epoxyphospholane **2** was found relatively resistant to typical nucleophilic ring opening by azide anion under standard conditions. Treatment of **2** with sodium azide in DMF at 80 °C caused decomposition of the starting material, whereas in refluxing ethyl alcohol[11] or acetonitrile in the presence of cerium chloride[12] no reaction occurred. Trimethylsilyl azide in the presence of a catalytic amount of salen–Cr[13] or salen–Mn[14] complexes (2–10 mol %) is known to act as highly effective source of azide nucleophile. Surprisingly, these reagent systems were completely ineffective when applied to epoxyphospholane **2** and only starting material was recovered from the reaction mixtures.

The only catalysts we found effective for the opening of epoxide ring in epoxyphospholane **2** were Ti(O–*i*Pr)$_4$ itself and Ti(O–*i*Pr)$_4$ in the presence of TADDOL, or

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Table 1. Reaction of epoxide **2** with trimethylsilyl azide

Entry	Catalyst	Equiv (mol%)	Solvent	**3**, Isolated yield (%)	Ee (%)[a]
1	Ti(O–*i*Pr)$_4$	66	Benzene[b]	79	—
2	Ti(O–*i*Pr)$_4$/TADDOL	15	CH_2Cl_2	69	6
3	Ti(O–*i*Pr)$_4$/TADDOL	15	THF	67	10
4	Ti(O–*i*Pr)$_4$/TADDOL	15	Toluene	94	15
5	Salen–Al	2	THF	Traces	—
6	Salen–Al	5	THF	90	19
7	Salen–Al	10	TBME	75	9
8	Salen–Al	10	CH_2Cl_2	81	28[c]
9	Salen–Al	10	[bmim]PF_6	90	13
10	Salen–Al	10	[bmim]PF_6/[bmim]OTf[d]	76	18
11	Salen–Al	10	[bmim]BF_4	73	20
12	Salen–Al	10	[bmim]OTf	80	23

[a] Ees were determined by ^{31}P NMR in the presence of (*S*)-(+)-naproxen as chiral shift reagent.[17]
[b] Reflux, 90 min.
[c] $[\alpha]_D^{20}$ −20.3 (*c* 0.82, chloroform).
[d] [bmim]PF_6–[bmim]OTf, 6:1.

salen–Al complex [(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminoaluminium(III) chloride].[15] Table 1 presents the results of the reaction of the epoxyphospholane **2** with trimethylsilyl azide in the presence of the above catalysts. Entry 1 is a blank reaction without chiral additives and the result shows that in the presence of Ti(O–*i*Pr)$_4$ in refluxing benzene racemic azide **3** could be obtained in good yield. Addition of TADDOL as the chiral diol ligand gave the expected azide **3** in good to excellent yields (depending on the solvent used) but with low ees (entries 2–4). The best results were obtained when salen–Al complex was used as the chiral catalyst although relatively high amounts of catalyst were required for completion of the reaction. In the presence of 2 mol% of the catalyst only traces of product were detected (entry 5), whereas for 5–10 mol% of the catalyst chemical yields increased to 90% (entries 6–8). Enantiomeric excess of **3** depended on the solvent used and reached 28% ee for the reaction in dichloromethane (entry 8). The reaction carried out in ionic liquids gave high chemical yields of **3** but with only moderate ees. In contrast to Song et al.'s report[16] we did not observe any strong influence of the nature of the molten salts on the enantioselectivity of the reaction, although in hydrophilic [bmim]BF_4 and [bmim]OTf ionic liquids slightly higher ees were obtained in comparison with hydrophobic [bmim]PF_6 (entries 9–12).

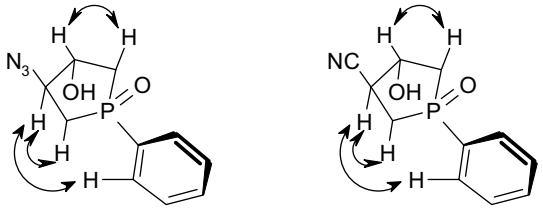
Next, we focused on the reaction of trimethylsilyl cyanide with epoxyphospholane **2**. We tried to use Ti(O–*i*Pr)$_4$[18] in the presence of TADDOL as a chiral ligand in THF or toluene solutions, however, only traces of the required product were detected. No reaction was observed when either Ti(O–*i*Pr)$_4$/salen, salen–Cr complex or pybox/$YbCl_3$[19] were used as the catalysts. Surprisingly, initial trials with salen–Al complex were also unsuccessful and only traces of product were detected in dichloromethane or THF solutions (Table 2, entries 1 and 2). Addition of molecular sieves to the THF solution markedly increased the yield of the reaction and cyanoalcohol **4** was obtained with moderate chemical yield and with good enantioselectivity with this catalyst (entry 3). Further improvement was achieved by switching to TBME as a solvent, which brought about the highest yield and asymmetric induction either with or without added molecular sieves (entry 4). It is interesting to note that when [bmim]PF_6 was used as a solvent the opposite enantioselectivity of the reaction was observed (entry 5). The reversed enantioselectivity in [bmim]PF_6 cannot be explained at the moment and it needs further studies. No reaction occurred in [bmim]BF_4 (entry 6). Racemic cyanoalcohol **4** could be efficiently obtained by treatment of epoxyphospholane **2** with Nagata's reagent,[20] Et_2AlCN, which gave the product in 81% isolated yield (Table 2, entry 7).[21]

The relative stereochemistry of the ring-opened products and *trans* array of 3,4-substituents were proven by checking close NOE contacts. In both cases contacts between *ortho*-proton of the phenyl group and the proton adjacent to azide or cyanide group were detected. For observed NOE interactions, see Scheme 2.

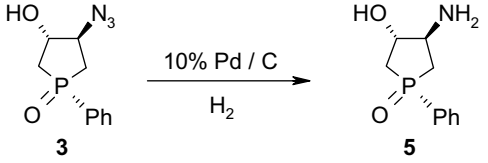
Table 2. Reaction of epoxide **2** with Et_2AlCN and trimethylsilyl cyanide

Entry	Catalyst	Equiv (mol%)	Solvent	Source of CN	**4**, Isolated yield (%)	Ee (%)[a]
1	Salen–Al	10	CH_2Cl_2	TMSCN	No reaction	—
2	Salen–Al	5	THF	TMSCN	Traces	—
3	Salen–Al	5	THF/MS 4 Å	TMSCN	20	65
4	Salen–Al	10	TBME	TMSCN	56	72[b]
5	Salen–Al	10	[bmim]PF_6	TMSCN	26	25
6	Salen–Al	10	[bmim]BF_4	TMSCN	Traces	—
7	—	—	Toluene	Et_2AlCN	81	—

[a] Ees were determined by ^{31}P NMR in the presence of (−)-*O*,*O*′-dibenzoyl-L-tartaric acid as chiral shift reagent.[17]
[b] $[\alpha]_D^{20}$ +28.3 (*c* 0.7, chloroform–methanol, 95:5).



Scheme 2. Selected NOE contacts in **3** and **4** as indicated by arrows.



Scheme 3. Only relative configurations of **3** and **5** are depicted.

Enantiomeric excess of the ring-opened products was determined by NMR spectroscopy using chiral shift reagents.[17] ^{31}P NMR spectra of **3** in the presence of (*S*)-(+)-naproxen exhibited resolution of the phosphorus signal and observed splitting was equal $\Delta\delta$ 6.6 Hz.[22] The signal of the major enantiomer of **3** was found at lower field. A similar treatment of **4** with (−)-*O*,*O*′-dibenzoyl-L-tartaric acid caused impressive splitting of the phosphorus signal reaching $\Delta\delta$ 52 Hz in this case. The signal of the dominating enantiomer of **4** (Table 2, entry 4) was found at higher field.

In conclusion, we have demonstrated that the enantioselective ring opening of achiral 3,4-epoxy-1-phenylphospholane oxide **2** by trimethylsilyl azide and trimethylsilyl cyanide in the presence of salen–Al complex can provide ready access to $-N_3$ and –CN functionalized enantioenriched P-stereogenic phospholane derivatives **3** and **4**. Simple reduction of azide **3** secures also prompt access to enantioenriched phospholane derivative **5** possessing versatile 1,2-aminoalcohol functionality (Scheme 3). Unfortunately to date we have been unable to obtain a suitable crystalline derivative for determination of the absolute configuration by X-ray analysis.

1. Experimental

Solvents were purified and dried according to literature methods. TLC was performed on Silica Gel HF-254 and column chromatography on Silica Gel 230–400 mesh (Merck). NMR spectra were recorded with a Varian AC-200 (200 MHz) and Bruker AM-500 (500 MHz) spectrometers in deuterochloroform ($CDCl_3$) with Me_4Si as internal standard. High resolution mass spectra (HR-MS) were measured with AMD-604 mass spectrometer. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded on Perkin–Elmer 1640 FT-IR spectrophotometer. [bmim]PF_6,[23] [bmim]BF_4[24] and [bmim]OTf[25] were prepared according to literature methods. **CAUTION!** Extreme caution should be exercised in the handling of organic azides of low molecular mass.

1.1. 4-Azide-3-hydroxy-1-phenylphospholane-1-oxide 3

1.1.1. Method A. To a solution of 3,4-epoxy-1-phenylphospholane-1-oxide **2** (291 mg, 1.5 mM) and trimethylsilyl azide (3.0 mM) in benzene (5 mL) tetraisopropoxytitanium (1.0 mM) was added and refluxed for 90 min. Water (0.5 mL) was added and stirred at room temperature for 30 min. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (hexane–ethyl acetate–methanol, 5:3:1 as eluent) to afford 280 mg (79%) of the title compound as white crystals.[26] Mp 111–112 °C. ^{1}H NMR ($CDCl_3$) δ: 4.59 (m, 1H, *J* 4.4, 9.5, 21.7 Hz, CHO), 4.25 (m, 1H, *J* 4.6, 10.3, 20.6 Hz, CHN), 2.48 (m, 2H, H-2,5), 2.26 (m, 1H, H-2′), 2.15 (m, 1H, H-5′). ^{13}C NMR ($CDCl_3$) δ: 132.76 (d, $J_{C,P}$ 2.8 Hz), 131.22 (d, $J_{C,P}$ 11.6 Hz), 129.30 (d, $J_{C,P}$ 12.4 Hz), 73.86 (d, $J_{C,P}$ 7.5 Hz, C–N), 66.57 (d, $J_{C,P}$ 8.0 Hz, C–O), 36.69 (d, $J_{C,P}$ 63.6 Hz, CH_2), 33.60 (d, $J_{C,P}$ 64.5 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 55.38. ν_{max} (film): 2106, 1438, 1255, 1186, 1169, 1136, 746 cm^{-1}. HR-MS (LSIMS) calcd for $C_{10}H_{13}N_3O_2P$ $[M+H]^+$: 238.0745. Found: 238.0738.

1.1.2. Method B. To a solution of 3,4-epoxy-1-phenylphospholane-1-oxide **2** (97 mg, 0.5 mM) and trimethylsilyl azide (1.0 mM) in dichloromethane (2 mL) salen–Al complex (30 mg, 0.05 mM) was added and stirred at room temperature for 24 h. The volatiles were evaporated under reduced pressure and the residue was dissolved in THF (1 mL), tetrabutylammonium fluoride (3 equiv) was added and stirred at room temperature for 2 h, evaporated to dryness and purified by column chromatography (hexane–ethyl acetate–methanol, 5:3:1 as eluent) to afford the title compound (96 mg, 81%).

1.1.3. Method C. 3,4-Epoxy-1-phenylphospholane-1-oxide **2** (97 mg, 0.5 mM), trimethylsilyl azide (1.0 mM) and salen–Al complex (30 mg, 0.05 mM) were dissolved in [bmim]PF_6 (0.8 mL) and stirred at room temperature for 24 h. Product was extracted with toluene and worked up as described for Method B.

1.2. 4-Cyano-3-hydroxy-1-phenylphospholane-1-oxide 4

1.2.1. Method A. To a solution of 3,4-epoxy-1-phenylphospholane-1-oxide **2** (971 mg, 5.0 mM) in toluene (5 mL) diethyl aluminium cyanide solution (1 M in toluene, 15 mL, 15 mM) was added and stirred at room temperature for 48 h. Water (0.5 mL) was added and stirred at room temperature for 30 min. The volatiles were evaporated under reduced pressure and the residue was purified by column chromatography (hexane–ethyl acetate–methanol, 5:3:1 as eluent) to afford 900 mg

(81%) of the title compound as white crystals. Mp 178–180 °C. ^{1}H NMR ($CDCl_3$+10% CD_3OD) δ: 4.82 (m, 1H, CHO), 3.23 (m, 1H, CHN), 2.65 (m, 1H, H-5), 2.58 (m, 1H, H-2), 2.39 (m, 1H, H-5′), 2.26 (m, 1H, H-2′). ^{13}C NMR ($CDCl_3$+CD_3OD) δ: 132.57 (d, $J_{C,P}$ 2.9 Hz), 131.04 (d, $J_{C,P}$ 98.3 Hz), 130.16 (d, $J_{C,P}$ 10.9 Hz), 128.86 (d, $J_{C,P}$ 12.7 Hz), 118.93 (d, $J_{C,P}$ 11.4 Hz, CN), 72.03 (d, $J_{C,P}$ 9.0 Hz, C–O), 36.52 (d, $J_{C,P}$ 64.1 Hz, CH_2), 35.93 (d, $J_{C,P}$ 8.9 Hz, *C*–CN), 31.40 (d, $J_{C,P}$ 63.1 Hz, CH_2). ^{31}P NMR ($CDCl_3$) δ: 54.85. ν_{max} (KBr): 2242, 1253, 1186, 1165, 1136, 1115, 756 cm^{-1}. HR-MS (EI) calcd for $C_{11}H_{12}NO_2P$ $[M]^+$: 221.0606. Found: 221.0601.

1.2.2. Method B. To a solution of 3,4-epoxy-1-phenylphospholane-1-oxide **2** (97 mg, 0.5 mM) and trimethylsilyl cyanide (1.0 mM) in TBME (1 mL) salen–Al complex (30 mg, 0.05 mM) was added, stirred at room temperature for 24 h and worked up as described for **3** (Method B) to afford 62 mg (56%) of the title compound.[26]

1.2.3. Method C. 3,4-Epoxy-1-phenylphospholane-1-oxide **2** (97 mg, 0.5 mM), trimethylsilyl cyanide (1.0 mM) and salen–Al complex (30 mg, 0.05 mM) were dissolved in [bmim]PF_6 (0.8 mL) and stirred at room temperature for 48 h. Product was extracted with toluene and worked up as described for **3** (Method B) to afford 62 mg (56%) of the title compound.

1.3. 4-Amino-3-hydroxy-1-phenylphospholane-1-oxide 5

A mixture of azide **3** [145 mg, 0.61 mM, $[\alpha]_D^{20}$ −20.3 (*c* 0.82, chloroform)] and 10% palladium on charcoal (200 mg) in methanol (2 mL) was kept overnight under hydrogen atmosphere (balloon), filtered through silica gel (methanol as eluent) and evaporated to dryness to yield 120 mg (98%) of aminoalcohol **5** as amorphous glass. $[\alpha]_D^{20}$ –6.4 (*c* 1.9, chloroform–methanol, 4:1). ^{1}H NMR ($CDCl_3$) δ: 4.20–4.58 (m, 4H), 3.55 (m, 1H), 2.52 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 75.50 (d, $J_{C,P}$ 10.8 Hz, C-4), 58.42 (d, $J_{C,P}$ 8.2 Hz, C-3), 36.96 (d, $J_{C,P}$ 62.6 Hz, CH_2), 36.52 (d, $J_{C,P}$ 62.0 Hz, CH_2). HR-MS (ESI) calcd for $C_{10}H_{15}NO_2P$ $[M+H]^+$: 212.0835. Found: 212.0847.

Acknowledgements

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21. In all cases studied no competing isocyanide formation was observed.
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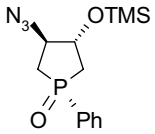
26. Usually, the mixtures of ring-opened products and corresponding trimethylsilyl derivatives were obtained. Typically, the products were isolated as the free hydroxy derivatives. One-pot desilylation procedure by TBAF treatment of the crude reaction mixture, as described in Method B, was the most effective for separation of desired products and removing of the traces of salen–Al complex. In one case, an analytical sample of 4-azide-3-*O*-trimethylsilyl-1-phenylphospholane-1-oxide **6** was isolated by

column chromatography (hexane–ethyl acetate–methanol, 5:3:1 as eluent) of the crude reaction mixture and was characterized by NMR spectroscopy: ^{1}H NMR ($CDCl_3$) δ: 4.48 (m, 1H, CH), 4.02 (m, 1H, CH), 2.48 (m, 2H, CH_2), 2.13 (m, 2H, CH_2), 0.21 (s, 9H, $SiMe_3$). ^{13}C NMR ($CDCl_3$) δ: 75.04 (d, $J_{C,P}$ 10.1 Hz, CN_3), 66.62 (d, $J_{C,P}$ 9.5 Hz, COH), 37.53 (d, $J_{C,P}$ 62.3 Hz, CH_2), 33.70 (d, $J_{C,P}$ 62.5 Hz, CH_2), 0.39 (s, $SiMe_3$).



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