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# Asymmetric synthesis of chiral *N*-(1-methylbenzyl)aminophosphines

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**Abstract**—The reactions of chlorophosphines **1** with (*S*)- or (*R*)-1-methylbenzylamines **2** proceed stereoselectively to give *N*-(1-methylbenzyl)aminophosphines **3**, which were isolated as crystalline borane complexes with 100% diastereomeric purity. The absolute configuration of the new chiral compounds was established by X-ray analysis and chemical extrapolation. 

Chiral trivalent organophosphorus compounds having a sterogenic phosphorus centre are important subjects of investigation due to the widespread use of these compounds as ligands for transition metal catalysis. The numerous patented chiral phosphines and aminophosphines are proof of the interest in such catalytic reactions from the industrial world.[2,3]

A few years ago, we reported a method for the asymmetric synthesis of phosphinic and phosphinous acid esters using the reaction of chiral alcohols with racemic nonsymmetrically substituted chlorophosphines in the presence of tertiary bases.[4] Proceeding with these studies, we have examined the reaction of the chlorophosphines **1** with the (*S*)- or (*R*)-enantiomers of *N*-(1-methylbenzyl)amine **2**, resulting in the formation of diastereomerically enriched *N*-(1-methylbenzyl)-aminophosphines **3** which, upon treatment with borane, provide the enantiomerically pure aminophosphines **3** (Scheme 1).

The diastereoselective reaction of chiral amines with phosphorus(III) chlorides has not been described previously, although the reaction of the amines **2** with phosphorus(V) chlorides has literature precedence.[5,6]

The stereoselectivity of the reaction between chlorophosphines **1** and *N*-(1-methylbenzyl)amine **2** in the presence of tertiary bases depends strongly on the reaction conditions and the nature of the base, solvent, temperature and ratio of starting reagents all affect the stereochemical outcome (Scheme 1). Under certain conditions this reaction proceeds with sufficient stereoselectivity to give diastereomerically enriched aminophosphines **3** (Scheme 1, entries 1 and 12). The aminophosphines **3** are colorless liquids that can be distilled under vacuum. The yields of aminophosphines after distillation are 75–80%.

The subsequent treatment of aminophosphines **3a** with borane in tetrahydrofuran (THF) leads to the formation of the stable crystalline adduct **4** in essentially quantitative yield. The complexes **4** were then purified by crystallization from hexane. $^{1}H$, $^{13}C$ and $^{31}P$ NMR analyses of the borane complex **4a** indicated the formation of only one diastereomer.[7] The $BH_3$ group of the phosphine–borane complex **4a** was removed on treatment with a large excess of diethylamine to furnish the initial aminophosphine **3a** in 100% stereochemical purity.[8] This reaction has been proven to proceed in a stereospecific manner with retention of configuration.[9,10]

The reaction permits facile access to enantiomerically pure aminophosphines **3**, which are potential starting materials for the synthesis of numerous chiral organophosphorus compounds (Scheme 2).

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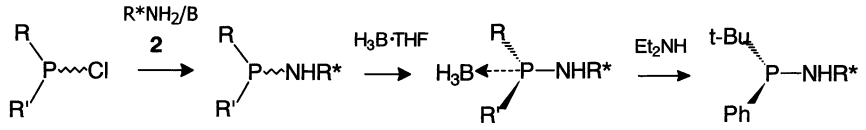
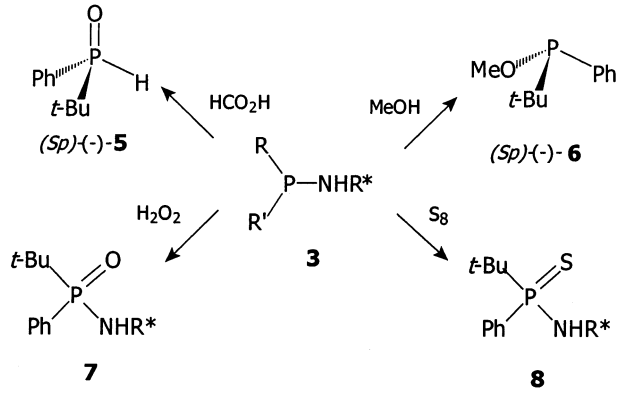



R*= (*S*)-CH(Me)Ph; R=*t*-Bu, R′=Ph (a); R= *t*-Bu, R′=*i*-Bu (b); R=Ms=2,4,6-$(Me)_3C_6H_2$, R′=Ph (c).

| Compd | R | R′ | Solvent | B[a)] | Ratio of 1:2:B | *dr* [b,c)] |
|---|---|---|---|---|---|---|
| **3a** | *t*-Bu | Ph | Benzene | TEA | *1:1:1* | 90:10 |
| **3a** | *t*-Bu | Ph | Benzene | TEA | *1:2:1* | 82:18 |
| **3a** | *t*-Bu | Ph | Benzene | TEA | *1:1:10* | 79:21 |
| **3a** | *t*-Bu | Ph | *Ether* | TEA | 1:1:1 | 88:12 |
| **3a** | *t*-Bu | Ph | *Hexane* | TEA | 1:1:1 | 80:20 |
| **3a** | *t*-Bu | Ph | *THF* | TEA | 1:1:1 | 82:38 |
| **3a** | *t*-Bu | Ph | Toluene | *TEA* | 1:1:1 | 84:16 |
| **3a** | *t*-Bu | Ph | Toluene | *MBA* | 1:1:1 | 82.5:17.5 |
| **3a** | *t*-Bu | Ph | Toluene | *DABCO* | 1:1:1 | 75:25 |
| **3a** | *t*-Bu | Ph | Toluene | *DBU* | 1:1:1 | 58:42 |
| **3b** | *t-Bu* | *i-Bu* | Benzene | TEA | 1:1:1 | 70:30 |
| **3c** | *Ph* | *Ms* | Benzene | TEA | 1:1:1 | 75:25 |

[a)] TEA=triethylamine; MBA=1-methylbenzylamine; DBU=diazabicycloundecene; DABCO= diazabicyclooctane.
[b)] At +20°C. [c)] Determined by $^{31}P$ NMR: $\delta_P$, ppm 49.9; 47.24 (**3a**); 29.09 and 29.65 (**3c**).

**Scheme 1.** The asymmetric synthesis of aminophosphines **3**.




**Scheme 2.** R* = CH(Me)Ph.

Thus, the ($R_p$,*S*)-aminophosphine **3a** was allowed to react with methanol to give the methyl (*S*)-(−)-*tert*-butylphenylphosphinate **5**. The hydrolysis of ($R_p$,*S*)-*N*-(1-methylbenzyl)amino-*t*-butylphenylphosphine **3a** in aqueous dioxane (80°C, 12 h) or acidolysis of **3a** with formic acid in toluene (15–30 min, 0°C) resulted in the formation of optically active (*S*)-(−)-*t*-butylphenylphosphine oxide **5**.[11] The specific rotation and other physical data for compound **5**, synthesized by us, and of (*S*)-(−)-*t*-butylphenylphosphine oxide, described in the literature, are identical.[12a–c]

The oxidation of aminophosphine ($R_p$,*S*)-**3a** by hydrogen peroxide in dioxane afforded only the ($S_p$,*S*)-diastereomer of aminophosphine oxide **7a** in a very good yield. The oxidation of the ($R_p$,*S*)+($S_p$,*S*)-diastereomer mixture **3a** using the same conditions provided a diastereomeric mixture of ($S_p$,*S*)- and ($R_p$,*S*)-aminophosphine oxides **7a**.

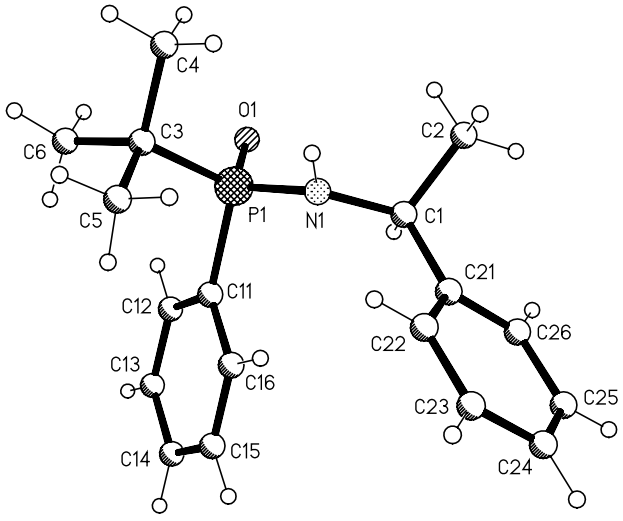



**Figure 1.**

The diastereomers **7** were separated by flash-chromatography. The products ($S_p$,*S*)- and ($R_p$,*S*)-**7** were crystalline[13,14] and a single crystal X-ray structural analysis established the absolute configuration of ($S_p$,*S*)-**7** (Fig. 1).[15] The thionation of the compounds **3a** gave the pure ($S_p$,*S*)-diastereomer of the phosphine sulfide **8**, which was isolated by crystallization from hexane as a colorless stable solid in ~100% diastereoisomeric purity.[16,17]

In summary, we have developed an accessible method for the preparation of chiral aminophosphines, which can be used as starting compounds for the asymmetric synthesis of organophosphorus compounds or as chiral ligands. We are currently studying the borane complexes **4** as chiral catalysts for the asymmetric reduction of C=O and C=N groups and the results of these studies will be reported in due course.

## Acknowledgements

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## References

1. Andrushko, N. *Ph.D. Thesis*; Institute of Bioorganic Chemistry, National Academy of Sciences of the Ukraine: Kiev, 2002; pp. 1–140.
2. (a) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279–1332; (b) Kolodiazhnyi, O. I. In *Advances of Asymmetric Synthesis*; New Achievements in Asymmetric Synthesis of Organophosphorus Compounds; Hassner, A., Ed.; JAI Press: Stamford, London, 1998; Vol. 3, Chapter 5, pp. 273–357.
3. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
4. (a) Kolodiazhnyi, O. I.; Grishkun, E. V. *Tetrahedron: Asymmetry* **1996**, *7*, 967–970; (b) Kolodiazhnyi, O. I.; Grishkun, E. V. *Phosphorus Sulfur Silicon* **1996**, *115*, 115–124.
5. Hamor, Th. A.; Jennings, W. B.; Lovely, C. J.; Reeves, K. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 843–849.
6. Burns, B.; King, P. N.; Tye, H.; Studley, J. R.; Gamble, M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1027.
7. **Data for borane complex, 4a**: Yield 90%, mp 140–141°C (hexane). $[\alpha]_D$ +24.5 (*c* 0.01, $CH_2Cl_2$). $^{31}P$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 69.76, br.d ($^1J_{BP}$ 42.93). $^1H$ NMR ($\delta$, ppm, *J*, Hz, $CDCl_3$) 0.2–2, m ($BH_3$); 1.01, d [$^3J_{HP}$ 14.16, $(CH_3)_3C$]; 1.50, d ($^3J_{HH}$ 6.72, $CH_3$); 2.07, br.d ($^2J_{HP}$ 16.0, NH); 4.45, m (CHN); 7.10–7.40, m ($C_6H_5$). $^{13}C$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 24.57, d [$^2J_{CP}$ 2.76, $(\underline{C}H_3)_3C$]; 25.57, d ($^3J_{CP}$ 5.20, $\underline{C}H_3CHN$); 30.69, d [$^1J_{CP}$ 43.40, $(CH_3)_3\underline{C}$]; 52.47, d ($^2J_{CP}$ 2.01, CHN); 126.10, s; 126.94, s; 127.58, d, $J_{CP}$ 9.50; 130.37, d, $J_{CP}$ 2.50; 130.75, d, $J_{CP}$ 46.80; 131.94, d, $J_{CP}$ 9.40 ($C_6H_5$).
8. **Data for ($S_p$,*S*)-3a**: Yield 50%, bp 130–135°C (0.02 mmHg). $^1H$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$): 0.81, d [$^3J_{HP}$ 7.0, $CH_3C$]; 1.60, m (NH); 1.45, d [$^3J_{HH}$ 14.0, $(CH_3)_3C$]; 3.54, m (CHN); 7.10–7.33, m ($C_6H_5$). $^{31}P$ NMR ($\delta$, ppm, $CDCl_3$) 49.00.
9. (a) Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655–660; (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252.
10. (a) Juge, S.; Stephan, M.; Laffitte, J. A.; Genet, J. P. *Tetrahedron Lett.* **1990**, *31*, 6357–6360; (b) Juge, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783.
11. **Data for (*S*)-(−)-6**: Yield 80%, $[\alpha]_D$ −44.6 (*c* 1, toluene), {lit. $[\alpha]_D$ −40.45 (*c* 1.78, MeOH)[12]}. $^1H$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 1.018, d [$J_{HH}$ 17, $(CH_3)_3C$]; 7.05–7.95, m ($C_6H_5$); 5.29, d ($^1J_{PH}$ 454, PH). $^{31}P$ NMR ($\delta$, ppm, *J*, Hz; $CDCl_3$) 48.17, d ($^1J_{PH}$ 454 Hz).
12. (a) Skrzypczynski, Z.; Michalski, J. *J. Org. Chem.* **1988**, *53*, 4549–4551; (b) Drabowicz, J.; Lyzwa, P.; Omelanczuk, J.; Pietrusiewicz, K. M.; Mikolajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2757–2763; (c) Haynes, R. K.; Freeman, R. N.; Mitchel, C. R.; Vonwiller, S. C. *J. Org. Chem.* **1994**, *59*, 2919–2921.
13. **Data for ($S_p$,*S*)-7**: Yield 80% (summary). $[\alpha]_D$ −82.5 (*c* 1, ethanol), mp 171–172°C (ethyl acetate). $^1H$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 1.01, d [$J_{HH}$ 14.8, $(CH_3)_3C$]; 1.33, d ($J_{HP}$ 7.0, $CH_3$); 2.80, br (NH); 4.44, br ($J_{HH}$ 8, CH); 7.19–7.4, m; 7.87, m ($C_6H_5$). $^{31}P$ NMR ($\delta$, ppm; $CDCl_3$): $\delta_P$ 41.32. The absolute configuration of ($S_p$,*S*)-**7** was determined by X-ray analysis (see Fig. 1).
14. **Data for ($R_p$,*S*)-7**: Yield 5% (summary). $[\alpha]_D$ −125.5 (*c* 1, ethanol), mp 142–144°C (heptane). $^1H$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 1.04, d [$^3J_{HP}$ 14.4 $(CH_3)_3C$]; 1.48, d ($^3J_{HH}$ 7.4, $CH_3C$); 2.76, dd (*J* 7.0, NH); 4.17, m (CH); 7.13–7.57 ($C_6H_5$); $^{31}P$ NMR ($\delta$, ppm; $CDCl_3$) 42.86.
15. **Data for ($S_p$,*S*)-8**: Yield 50%, $[\alpha]_D$ −66 (*c* 2.5, ethanol), mp 105–106°C (hexane). $^1H$ NMR ($\delta$, ppm; *J*, Hz; $CDCl_3$) 1.15, d [$J_{HP}$ 16.2, $(CH_3)_3C$]; 1.5, d ($^3J_{HH}$ 6.6, $CH_3$); 2.3, br (NH); 4.4, dq ($^3J_{HH}$ 6.6, $^3J_{HP}$ 8 CHN); 7.2, m; 7.93, m ($C_6H_5$). $^{31}P$ NMR ($\delta$, ppm, $CDCl_3$) 78.10.
16. All new compounds gave satisfactory microanalytical data. **3a**: Anal. calcd for $C_{18}H_{24}NP$: N, 4.91; P, 10.85. Found: N, 4.85; P, 10.91%. **4a**: Anal. calcd for $C_{18}H_{27}BNP$: N, 4.68; P, 10.35. Found: N, 4.71; P, 10.46%. **7**: Anal. calcd for $C_{18}H_{24}NOP$: N, 4.65; P, 10.28. Found: N, 4.67; P, 10.42%. **8**: Anal. calcd for $C_{18}H_{24}NPS$: N, 4.41; P, 9.76. Found: N, 4.45; P, 9.62%.
17. **Crystal data for (*S*,*S*)-7**: $C_{18}H_{24}NOP$, monoclinic, space group $P2_1$, $a$=867.90(10), $b$=1908.8(2), $c$=1036.71(12) pm, $\beta$=90.211(3)°, $V$=1.7175(3) nm$^3$, $Z$=4, $\mu$(Mo–K$\alpha$)=0.159 mm$^{-1}$, $T$=−130°C. *Data collection*: colourless prism 0.37×0.24×0.15 mm, Bruker SMART 1000 CCD diffractometer. Measured reflections 14595 ($2\theta_{max}$ 52°), 6045 independent ($R_{int}$ 0.0358). Structure solution: direct method, anisotropic refinement on $F^2$ (program system: SHELXL-97, Sheldrick, G. M.; University of Göttingen). The structure was refined as a pseudo-merohedral twin with twinning matrix −1 0 0 0 −1 0 0 0 1 (associated with the $\beta$ angle of ca. 90°); the BASF value refined to 0.437(1). The Flack parameter was refined to −0.05(8). Hydrogen atoms included using a rigid (methyls) or a riding (others) model. Final $wR_2$ 0.0720, with $R_1$ 0.0375, for 394 parameters and three restraints; *S* 1.013; max. $\Delta\rho$ 0.223 e nm$^{-3}$. Crystallographic data (excluding the structure factors) for the structure have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Rd., GB-Cambridge CB2 1EZ, as supplementary publication no. CCDC 195666. Copies may be obtained free of charge on application to the Director (Telefax: Int. +12 23 33 60 33; http:\\www.deposit@ccdc.cam.ac.uk).