A New and Highly Enantioselective Synthetic Route to P-Chiral Phosphines and Diphosphines

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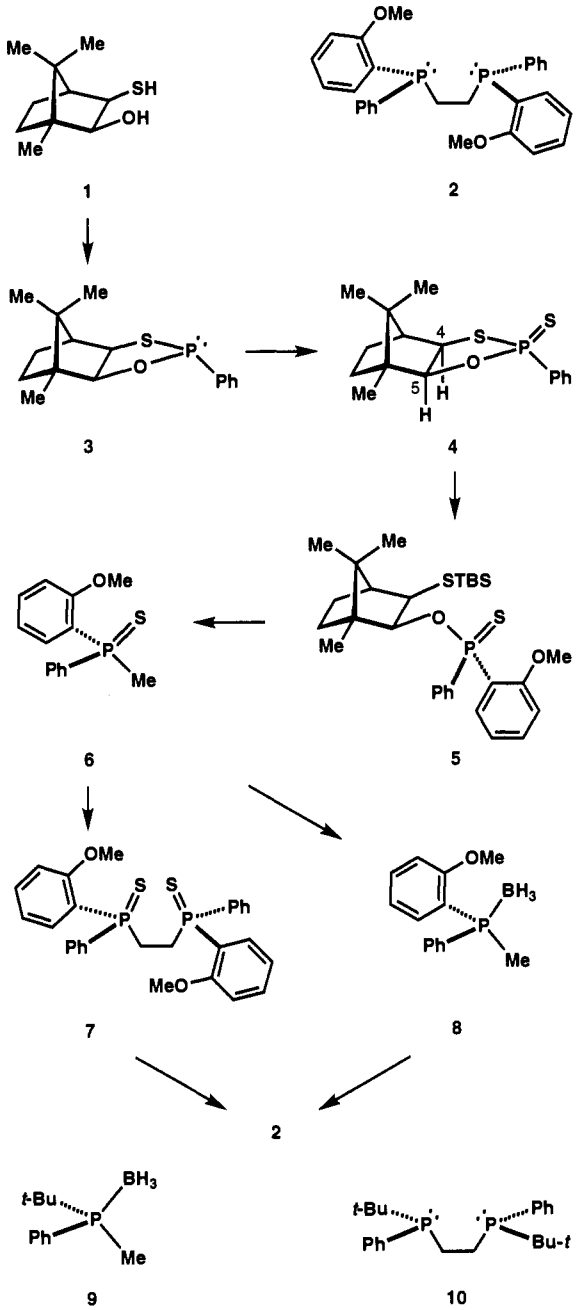
Progress in the development of transition-metal catalysts for enantioselective reactions, especially hydrogenation processes, heavily depends on the availability of suitable chiral phosphine or diphosphine ligands.[1] Yet, despite the critical importance of P-chiral phosphines, the methodology for their enantioselective synthesis in high enantiomeric excess (ee) and without resolution or separation of diastereomers remains relatively undeveloped.[2] We describe herein an effective enantioselective synthesis of chiral tertiary phosphines of type ArR_1R_2P or Ar_1Ar_2RP which meets the following criteria: (1) predictable absolute configuration of product phosphine, (2) accessibility of either phosphine enantiomer, (3) high enantiomeric purity (>97% ee), and (4) a readily available, recoverable, and reusable chiral reagent. To achieve these goals, a chiral bifunctional reagent was required which would allow the *diastereoselective* formation of a cyclic phospholidine intermediate in which two heteroatoms attached to phosphorus can be displaced stereospecifically by nucleophilic aryl or alkyl groups but with a large difference in rate for the first and second displacement. Oxygen and sulfur proved to be ideal heteroatoms on the framework of the readily prepared and known[3] camphor derivative **1**. Although in principle stereospecific displacement steps could be obtained with either P(III) or P(V) substrates, in practice the use of the latter (in the form of thiophosphonate esters) may be easier experimentally because of the lower sensitivity of P(V) intermediates to oxygen.

The effectiveness of the new route to chiral phosphines is clearly illustrated by the enantioselective synthesis of the industrially important diphosphine (–)-(*R,R*)-DIPAMP (**2**) (Scheme I).[1b] Reaction of **1** with phenyldichlorophosphine under argon in toluene at 0–20 °C for 1 h and at 110 °C for 50 h afforded stereospecifically the oxathiaphospholidine **3** in a thermodynamically controlled process. At shorter reaction times, the reaction mixture contained both **3** and the less stable *endo*-P-C_6H_5 diastereomer. Compound **3** was obtained in 78% yield after short-path distillation (220 °C at 0.25 mm) as a colorless liquid which is sensitive to air and moisture but which can be stored at –20 °C under dry nitrogen as the neat liquid. Reaction of **3** with S_8 in toluene at 80 °C for 2 h gave the crystalline thiophosphonate **4**, which could also be prepared more conveniently in a one-flask procedure from

Scheme I



1 in 80% overall yield, mp 114–114.5 °C (from EtOAc–hexane), $[\alpha]^{23}_D$ +68.7° (*c* = 1, CH_3OH). The *cis* arrangement of the phenyl group and the two hydrogen substituents (at C(4) and C(5)) of the oxathiaphospholidine ring in **4** was clearly demonstrated by the observation of 4.8 and 4.0% NOE effects between the two equivalent *ortho* hydrogens attached to the phenyl and H(5) and H(4), respectively. Treatment of **4** in toluene with 2 equiv of *o*-anisyllithium[4] (in THF–ether–hexane) at –78 °C for 1.5 h and further reaction with *tert*-butyldimethylsilyl (TBS) triflate at –78 °C for 45 min provided after extractive isolation thiophosphinate ester **5** as a colorless solid (91%), mp 130.5–131.5 °C, $[\alpha]^{23}_D$ +4.2° (*c* = 1.0, CH_2Cl_2). Thiophosphinate ester **5** was transformed into the chiral tertiary phosphine sulfide **6** via the following sequence of operations (all under Ar to prevent formation of the disulfide of **1**[3]): (1) reaction with 7 equiv of methyllithium and 7 equiv of tetramethylethylenediamine (TMEDA) in ether at 20 °C for 40 min; (2) quenching with 8 equiv

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(3) (a) Goodridge, R. J.; Hambley, T. W.; Haynes, R. K.; Ridley, D. D. *J. Org. Chem.* **1988**, *53*, 2881. (b) Hung, S.-M.; Lee, D.-S.; Yang, T.-K. *Tetrahedron: Asymmetry* **1990**, *1*, 873. The route to **1** from (+)-camphor involves (1) reaction with LDA and thiobenzyl tosylate (95%) to form α-(*exo*)-(*S*)-benzylcamphor, (2) carbonyl reduction with DIBALH in CH_2Cl_2 (96%), and (3) debenzylation (Na/NH_3, 70%). The thiol **1** undergoes ready oxidation to the corresponding disulfide (even in hexane solution) and should be handled and stored under N_2. Thiol **1** can be regenerated from the disulfide by reduction with $LiAlH_4$ in THF.

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of air-free methanol in the cold; (3) extractive isolation and treatment of the resulting crude solid mixture with 10 equiv of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C (to effect TBS ether cleavage to form **1**); (4) extractive isolation and treatment of the resulting mixture with hexane to give crystalline phosphine sulfide **6** (80%), mp 114–114.5 °C, $[\alpha]^{23}_D$ –7.9° (c = 1, CH_3OH); and (5) silica gel chromatography to give an additional 7% of **6** and recovered mono thiol alcohol **1** (>80%). The enantiomeric purity of **6** was determined to be >99% by HPLC analysis using a 25-cm Daicel AD column, 20% *i*-PrOH–hexane, 1 mL/min (peak at 11.34 min; no peak corresponding to *ent*-**6** at 8.86 min). Deprotonation of **6** (1.3 equiv of *sec*-BuLi in THF at –60 °C for 2.5 h) and oxidative coupling *in situ* (3 equiv of cupric pivalate at –60 °C to 23 °C over 1.5 h) afforded (+)-(*S*,*S*)-DIPAMP bis-sulfide **7** (65–75% after recrystallization from butyl acetate), mp 190–190.5 °C, $[\alpha]^{23}_D$ +82.8° (c = 1, CH_2Cl_2). Desulfurization of **7** was effected by reaction with Si_2Cl_6[5] in benzene at reflux for 30 min to form **2**, which after subsequent treatment with BH_3–THF was isolated in 87% yield as the bis-BH_3 adduct, mp 162.5–164 °C, $[\alpha]^{23}_D$ +66.5° (c = 1.3, $CHCl_3$) [lit. for the enantiomer,[2c] mp 162.5–163 °C, $[\alpha]^{23}_D$ –70° (c = 1.3, $CHCl_3$)]. A reference sample of the bis-BH_3 adduct of **2**, which was prepared from an authentic sample of (–)-(*R*,*R*)-DIPAMP (courtesy of Dr. W. S. Knowles), had mp 162–163.5 °C, $[\alpha]^{23}_D$ +66.1° (c = 1.3, $CHCl_3$). Analytical HPLC analysis of synthetic and reference samples of the bis-BH_3 adduct of **2** using a 25-cm Daicel AD column, 2.5% *i*-PrOH–hexane, 1 mL/min, showed only a single peak at 31.75 min and no trace of a peak corresponding to the (*S*,*S*)-enantiomer at 29.29 min, indicating >99% enantiomeric excess.

Similarly, tertiary phosphine sulfide **6** (>99% ee) was converted to the corresponding BH_3 adduct of (–)-(*R*)-*o*-anisylphenylmethylphosphine (**8**, 85% yield), mp 71–72 °C, $[\alpha]^{23}_D$ –25.5° (c = 1.5, CH_3OH), 97.4% ee by HPLC analysis with a 25-cm Daicel OJ column, 40% *i*-PrOH–hexane, 1 mL/min (10.04- and 17.57-min elution times for (*R*) and (*S*) enantiomers, respectively). Deprotonation of **8** (*sec*-BuLi), coupling with $CuCl_2$, and base treatment converts **8** to diphosphine **2**.[2c]

The stereochemistry of the synthesis of **6** from **4**, which corresponds to one displacement reaction with retention and one diplacement with inversion, requires comment. The first step, **4** → **5**, is formulated as the retention step on the basis of analogous cases of 5-membered cyclic phospholidine derivatives.[2d,6–9] This displacement presumably occurs by addition of the nucleophile at an apical position of a trigonal bipyramid (opposite oxygen), pseudorotation, and loss of the leaving group S^- from an apical position.[7–9] Displacement of sulfur instead of oxygen in this step is probably a consequence of the weakness of the P–S bond as compared with the P–O bond.

The synthesis of (+)-(*S*)-*tert*-butylmethylphenylphosphine–BH_3 adduct **9** and diphosphine **10** directly from oxathiaphospholidine **3** illustrates the shorter route to P-chiral phosphines via P(III) intermediates. Reaction of **3** in ether with 1.5 equiv of *t*-BuLi–3 equiv of TMEDA at –78 °C for 3 h, followed by 3 equiv of CH_3Li–3 equiv of TMEDA at –78 °C initially and –78 °C to 20 °C over 3 h, followed by treatment with BH_3–THF and extractive isolation (all under Ar) afforded phosphine–borane adduct **9** (65%, plus 76% recovered **1**), mp 50–51 °C, $[\alpha]^{23}_D$ +8.1° (c = 1, CH_3OH), [lit. for the (*R*)-enantiomer,[2c] mp 52.5–53 °C, $[\alpha]^{23}_D$ –8.2° (c = 1, CH_3OH)]. The enantiomeric purity of **9** was determined as 97.5% by HPLC analysis using a 25-cm Daicel AS column, 1% *i*-PrOH–hexanes, 1 mL/min, 13.30 min (major), 11.20 min (minor). Deprotonation of **9** and oxidative coupling provides diphosphine **10**, as reported previously.[2c] The transformation **3** → **9** involves one displacement with retention and one with inversion, as noted above for **4** → **6**.[10]

High *exo* diastereoselectivity in the synthesis of P-substituted oxathiaphospholidines from **1** seems to be general. Analogs of oxathiaphospholidine **3** with methyl or diethylamino instead of phenyl were readily prepared with complete diastereoselectivity (*exo* CH_3 or Et_2N attached to P) by using equilibrating conditions with the reagents $MeP(NEt_2)_2$ or $(Et_2N)_3P$.

The methodology reported herein shows promise for the synthesis of a wide range of P-chiral phosphines and diphosphines of high enantiomeric purity and should, therefore, accelerate the development of phosphine-based enantioselective transition-metal catalysts.

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Supplementary Material Available: Characterization data for compounds **3**–**7** and experimental procedures for **3** and **9** (2 pages). Ordering information is provided on any current masthead page.

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