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Optically Active Phosphines by Asymmetric Reduction of Racemic Phosphine Oxides

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The known synthetic procedures for preparing optically active phosphines with chirality at phosphorous are based on a stereospecific conversion of optically active precursors usually obtained via the classical methods of fractional crystallization. In this paper are reported some examples of racemic phosphine oxides reduction by chiral nonracemic aluminum hydride derivatives leading to optically active phosphines. The dependence of the reduction mechanism on the reaction conditions are also discussed.

Introduction

Until recently the studies on the synthesis of optically active alkyl, aryl phosphines with chirality at the phosphorous atom were mainly devoted to the experimental verification of the stability of the tervalent phosphorous structure towards piramidal inversion.

During the last years however, the reported successful results[1–3] in the field of catalytic asymmetric hydrogenation by using Rh complexes with optically active phosphines opened to such compounds a wide area of application.

Reported pathways leading to the synthesis of chiral non racemic phosphines are cathodic reduction[4] or base catalyzed hydrolysis[5] of optically active phosphonium salts, reduction of optically pure phosphine oxides with trichlorosilane[6] or perchloropolysilanes.[7]

These methods require the preliminary resolution of the racemic phosphine oxide, usually carried out via fractional cristallization of diastereomeric pairs, and differ among them in the choice of the agent able to convert the resolved precursor into the corresponding phosphine with the maximum degree of stereospecificity.

They cannot therefore be regarded as asymmetric syntheses, as has been pointed out elsewhere.[8]

The possibility of obtaining optically active phosphines by asymmetric reduction of racemic precursors would be in fact a rather interesting topic, bound both to the investigation of the reaction mechanism and stereochemistry of the organic phosphorous compounds, and to the improvement of the synthetic procedures, providing a sound choice in terms of experimental simplification.

The preliminary requirement to approach such a problem is availability of a chiral agent highly stereoselective towards the racemic substrate and effective at the same time in converting the preferred enantiomer to the corresponding phosphine with high stereospecificity. However, the chemical stability of P(V) compounds requires either to proceed under drastic conditions (which induce racemization by thermally induced piramidal inversion), or to use strongly reducing agents, thus restricting the range of selection.

Moreover, the nucleophilic substitution at tetracoordinated phosphorous, either by direct substitution (S_N2) or by addition elimination mechanism, proceeds through the stereochemically labile phosphoranic intermediate, undergoing autoracemization via pseudorotation.[9] For instance the LAH reduction of optically active phosphine oxides[10] leads always to racemic phosphines*, and the total stereospecificity which is observed when using $HSiCl_3$ (or Si_2Cl_6) is explained in terms of different lifetimes of the pentacoordinated species in the two instances.

Although the above considerations would induce to rule out the LAH, as well as any other aluminum hydride derivative, as intrinsically unsuitable reducing agents, in despite of their remarkable efficiency under mild conditions, we have investigated in the present work the stereochemical course of the reduction of racemic phosphine oxides using optically active derivatives of aluminum hydride with the following purposes: a) to evaluate the extent, if any, of asymmetric induction shown by such reagents; b) to test whether the asymmetry of the chiral hydride could exert a favourable effect in limiting the rate of pseudorotation of the phosphoranic intermediate, and thus the epimerization at the phosphorous asymmetric centre, so as to stabilize one of the various predictable stereoisomeric forms with respect to the others.

* The only successful reported example[11] has indeed to be considered as an anomaly,[10] due to peculiar features of the phosphorous substituents.

Chiral Amino Alanes

The reducing agents used in this work represent a new class of optically active aluminum hydride derivatives. Their noteworthy effectiveness in performing asymmetric reduction of prochiral keto compounds has been recently reported by some of us.[12]

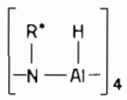
The amino alanes can be easily synthesized according to the following reactions:

1) $AlH_3 \cdot N(CH_3)_3 + R^*NH_2 \rightarrow (I) + 2H_2 + N(CH_3)_3$

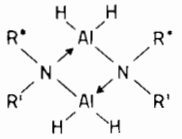
2) $AlH_3 \cdot N(CH_3)_3 + R^*NHR' \rightarrow (II) + H_2 + N(CH_3)_3$

3) $LiAlH_4 + R^*NHR' \cdot HCl \rightarrow (II) + 2H_2 + LiCl$

$(R^* = C_6H_5-\underset{\displaystyle H}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}}-,\ R' = -CH_3)$



(I)
Poly(S(−)phenethylamino) alane (PIA)

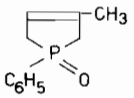


(II)
Methyl, S(−)phenethyl-aminoalane (DAA)

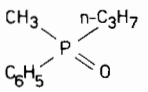
which recall the reported procedures[13,14] for the synthesis of the homologous achiral derivatives.

Peculiar to these compounds is their efficiency as reducing agents also under rather severe conditions, mainly due to their unusual solubility in the most various aprotic solvents (ethers, toluene, aliphatic hydrocarbons) even at temperatures down to −78° C. There is also to point out the ease of recovery of the asymmetric starting amine from the reaction mixture in fairly good yields with unaffected optical purity.

Our investigation has been mainly directed to the reduction of the racemic cyclic phosphine oxide (III)



(III)



(IV)

and, to a lesser extent to acyclic oxides, such as racemic methyl, n-propyl, phenyl phosphine oxide (IV).

It is known[15] that in the presence of cyclic substituents the number of allowed stereoisomeric P(V) intermediates is lowered and the energy barriers to the pseudorotation are at the same time increased. This would enhance the effects of a possible asymmetric induction, so as to make easier the preliminary investigation of the optimum reaction conditions.

Unfortunately there are no data about the absolute rotation of both the phosphine oxide (III) and the corresponding phosphine; our attempts to obtain the values either via spectroscopic methods[16] or by fractional cristallization procedures[17] have been so far unsuccessful. At the present stage however the missing data should not greatly affect our investigation, being the variation of the phosphine polarimetric values in the various experiments sufficient to give useful indications about the dependence of the asymmetric induction degree on the reaction conditions.

Results

Influence of the Alane/Substrate Concentration Ratio

The reduction of the cyclic phosphine oxide (III) has been carried out using PIA (I) at increasing concentration ratios (Table I).

The data show an increase of both the reaction rates and the optical purity of the phosphine as the concentration ratio is raised. This could in part be explained in terms of chemically induced racemization of the reaction product due to the permanence of the phosphine into the reaction medium. The thermal racemization can be excluded, for in a control experiment no optical activity decay was observed in a sample of chiral phosphine after refluxing in benzene for three hours, whereas samples of the phosphine isolated from the reaction mixture at different contact times show a decrease of the optical purity. Such effect has been already observed on using others reducing agents.[7]

However the sharp increase of the optical purity (Table I) which can be observed when going from low to high concentration ratios cannot be explained exclusively in terms of restricted racemization: this behaviour would suggest the existence of a rather complex overall reaction mechanism, with the participation of more than one chiral reducing unit to the asymmetric reduction.

Influence of the Temperature

The dependence of the reaction on the temperature has been investigated by carrying out the reduction at −20° C. The reported data, when compared to the ones obtained at +17° C, show that i) the rotation sign of the phosphine is reversed; ii) the reduction rate is faster, especially at lower concentration ratios; iii) the optical purity of the phosphine is in general

TABLE I.

Run No.	[AlH]ᵃ / [PO]	Time (min)	Yield[b] %	$[\alpha]_D^{25}$ Phosphine[c]
1	1	25	40	− 1.9
2	2	25	80	+ 4.0
3	3	25	80	+11.6
4	4	25	90	+14.6

[a] Active hydrogen amount determined by gasvolumetric analysis [b] Estimated by GLC. [c] Measured on pure undiluted phosphine samples.

higher and tends to be lowered in the presence of an excess of alane.

Discussion

To account for the dependence of the stereochemical course on the variation of both the reactants ratio and the temperature, the following interpretation is proposed.

It is admitted that the first step is the phosphine oxide complexation by the alane, followed by the hydridic hydrogen transfer from the latter to the substrate, through one of the following mechanisms:

a) unimolecular mechanism, in which the same Al–H unit contemporarily acts as a complexing and reducing agent;

b) bimolecular mechanism, in which the reduction of the complexed phosphine oxide is carried out by an "external" AlH unit, which could belong either to the same PIA molecule on which the substrate is complexed or, more likely, to another molecule.

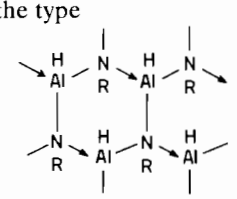
The above pathways are associated with opposite stereochemistry, the former one (unimolecular) involving retention of configuration of the obtained phosphine with respect to the precursor oxide, the latter one (bimolecular) occurring with inversion of configuration. The above assignements are proved to be correct on the basis of the following evidences. First of all the stereoselectivity of the PIA is steadily directed towards the preferred choice of the (–)enantiomer regardless of the experimental conditions: as a matter of fact, in all the reported reactions the recovered oxide (which has been in some cases isolated by quenching the reaction before going to completion) exhibited a slight positive rotation. Furthermore both the cyclic phosphine oxide and the corresponding phosphine have the same absolute configuration when exhibing the same rotation sign. This has been proved by H_2O_2 oxidation of a sample of partially resolved (+)phosphine (the oxidation is known[18] to occur with complete retention of configuration). The isolated reaction product was also positive.

By examining the experimental data in the light of the above hypoteses it is possible to conclude that the proposed reaction mechanisms are competitive and that the relative predominance is determined by the experimental conditions. The poor optical purity of the phosphine obtained when operating at low AlH/PO ratios, where the bimolecular mechanism is intrinsically unfavoured, indicates a contribution of the unimolecular pathway. The last one is on the contrary clearly prevailing at –20° C, and again the drop in the phosphine optical purity which is observed in the presence of an excess at the reducing species accounts for the contribution of the alternative competing bimolecular mechanism.

However, although it is apparent that no clear cut borderline exists between the pathways, other observations would support the proposed hypothesis.

At –20° C the equilibrium concentration of the intermediate adduct AlH-PO is probably increased thus increasing the observed reaction rate.

It is also to point out the effect which the decreasing of the temperature could exert on the mutual interactions between the PIA molecules in solution. It is known[14] that structures of the type $[-Al(H)N(R)-]_x$ can give rise to acid-base interactions in the Lewis's sense of the type



Therefore, when operating in the presence of non donor solvents, the lowered temperature, by enhancing the stability of such interactions, would also reduce the free motion of the reducing molecules thus rendering less favoured the bimolecular pathway. In order to study this effect, the reductions have been carried out using triethylamine–toluene mixture as a solvent, and the results (Table II) show, as expected, the remarkable influence of the donor solvent, although it is difficult at the present stage to rationalize the different stereochemical behavior of a "solvated" PIA molecule with respect to an "unsolvated" one. It is observed that the degree of overlapping of the two competing mechanisms is somehow reduced, the unimolecular one prevailing at stoichiometrical AlH/PO ratios and the bimolecular one prevailing in the presence of an excess of alane, regardless of the temperature. On the other hand, the presence of triethylamine gives rise to an unexpected increase of the reaction rate, especially when operating at +17° C in 1:1 AlH/PO ratios: as a matter of fact lower rate values were instead expected on the basis of the increased steric hindrance to the approach of the phosphine oxide molecule to the TEA complexed reducing unit. Such a behaviour accounts for the complexity of the reaction under investigation and makes apparent the need of further research in this field.

The study of chiral alanes other than PIA has been recently initiated by reducing the cyclic substrate (III) with DAA (II). The first results (Table III) show the predictable different behaviour of the latter as compared with PIA. The optical purity of the phosphine is in general lower and both the dependence of the optical activity on the concentration ratio and on the temperature are no longer observed.

To account for, several factors have to be considered: for instance, the different stereochemical environment of the reducing site in the two alanes, which will probably effect the degree of asymmetric induction. Also a

TABLE II.

Run No.	$\frac{AlH^a}{PO}$	Temperature	Solvent	Time, min	Yield[b] %	$[\alpha]_D^{25}$ Phosphine[c]
1	0.5	−20	toluene	8	70	−18.7
2	1	−20	toluene	8	70	−23.8
3	2	−20	toluene	8	70	−30.7
4	3	−20	toluene	8	90	−32.1
5	4	−20	toluene	8	90	−23.5
6	1	+17	toluene, TEA[d]	12	90	− 5.3
7	1	−20	toluene, TEA[d]	13	90	−16.0
8	4	+17	toluene, TEA[d]	20	90	+11.9
9	4	−20	toluene, TEA[d]	20	90	+12.4

[a, b, c] See footnote of Table I. [d] See experimental part.

TABLE III.

Run No.	$\frac{[AlH_2]^a}{[PO]}$	Temperature	Solvent	Reaction Time, min	Yield %	$[\alpha]_D^{25}$
1	0.5	+17	toluene	150	60	+3.10
2	2	+17	toluene	75	90	+8.4
3	4	+17	toluene	60	90	+7.6
4	2	−20	toluene	20	80	+6.6
5	2	−65	toluene	20	80	+5.0

[a, b, c] See footnote Table I.

reduction in the degree of long range intermolecular association is predictable in the case of DAA, although the effect cannot be completely ruled out, being the aluminum atom able to coordinate up to six ligands. And also a different reduction mechanism could be expected for a dihydrido species, as compared with the above proposed ones, thus involving a possible different stereochemical pathway. It is however to point out that a different behaviour was already observed[12] in the asymmetric reduction of prochiral ketones on using either PIA or DAA.

We wish finally to report some results in the reduction of the acyclic phosphine oxide (IV).

At +17°C the reduction product, either using PIA or DAA at concentration ratios ranging from 0.5 to 5 showed no detectable optical rotation.

On the contrary, when carrying out the reduction at −20°C with a four-fold excess of PIA the isolated pure phosphine (±30% yield) exhibited $[\alpha]_D^{25} = +3.95°$ (c = 5.05 toluene) which, compared with the absolute known rotation of the compound[4] corresponds to a 21.5 percent asymmetric induction.

On the basis of the above results, it is confirmed that chiral amino alanes are effective in performing the asymmetric reduction of phosphine oxides, thus providing, to the best of our knowledge, the first reported successful example in this field. It is our opinion that further studies in this area, and in particular the investigation of a larger number of chiral amino alanes will lead to an improvement of the optical purity of the chiral phosphines.

Experimental

The reactions have been carried out under nitrogen.

The solvents have been purified by refluxing over LAH and distilled under nitrogen prior to use.

LAH (Fluka pure grade) was used as purchased.

S(−)Phenethylamine (Fluka $[\alpha]_D^{25} = -44.5°$, neat) was stored under nitrogen and used as purchased.

S(−)Methyl phenethylamine has been prepared according to the literature.[19] $[\alpha]_{546}^{25} = -31°$ (c = 2.5, ethanol) for the hydrochloride, literature[20] $[\alpha]_{546}^{25} = -30.0°$ (c = 2.5, ethanol). M.p. 208°C, literature[20] 213°C. Analysis: $C_9H_{14}ClN$, calc N 8.16%, C 62.97%, H 8.16%; found N 8.27%, C 62.61%, H 8.00%.

(R,S)Methyl, n-propyl, phenyl phosphine oxide was obtained by reacting Methyl (methyl, phenyl) phosphinate[21], MePhP(O)OMe with n-propyl magnesium bromide. The phosphine oxide was purified by recristallization from Chloroform/n-hexane and identified by NMR analysis.

(R,S)3-Methyl, 1-phenyl phospholene 1-oxide[22] (III) was prepared according the literature from iso-

prene and phenyl dichlorophosphine and purified by distillation under reduced pressure; b.p. 155°C/0.01 mmHg (literature b.p. 173–4°C/0.7 mmHg) (yield 62.5%).

Trimethylaminato alane, $AlH_3 \cdot N(CH_3)_3$ was prepared from LAH and $N(CH_3)_3 \cdot HCl$ in ether,[21] the solvent removed and the compound isolated by sublimation at 50°C under high vacuum (yield 80%).

Poly (S(–)Phenethylimino) Alane

To a solution of $AlH_3 \cdot N(CH_3)_3$ in ether (0.87 mol in 800 ml ether) a equimolecular amount of S(–) Phenetilamine dissolved in 400 ml ether was added dropwise. The temperature was kept below +10°C (ice bath). The reaction flask is then maintained at room temperature for 3–4 hours during which a considerable amount of amine and hydrogen is evolved. The reaction is then completed by refluxing for 4–5 hours. The ether is removed by distillation, and the residue dissolved in 600 ml of dry benzene. The solution is warmed to 55–60°C to remove the last traces of amine, the solvent distilled under reduced pressure ($t° \leqq 50°C$). The viscous sticky residue is finally dried at room temperature under high vacuum (10^{-4}–10^{-5} mm) for several hours. The compound is thus obtained in the form of white light powder in nearly quantitative yield. Active hydrogen (determined according to standard gasvolumetric methods) 6.89 mgat/g, Aluminum (determined by EDTA complexometric titration) 6.43 mgat/g. Nitrogen (determined by the Kjeldahl method) 6.96 mgat/g. $[\alpha]_D^{25} = +34.5°$ (c = 4.95, benzene).

The average molecular weight, by which a polymerization degree of 4 is calculated, was determined by mass spectrometry.[24]

Methyl S(–)Phenylamino Alane

To a suspension of LAH (0.650 mol in 1200 ml ether) the solid Methyl S(–)phenethyl amine hydrochloride (0.570 mol) was slowly added. A strong hydrogen evolution is observed. The reaction is controlled by cooling the flask at 0–5°C. At the end of the addition the reaction is allowed to go to completion at room temperature under vigorous stirring for 2 hours. Lithium chloride and part of the unreacted LAH are removed by filtration. The clean colourless ether solution is brought to dryness and the white residue is then dissolved in dry benzene (500 ml), warmed at 50–55°C for 30 min and again filtered (G IV) to remove the last traces of LAH.

The benzene solution is evaporated to dryness at a temperature not exceeding 50/55°C. The white residue is then dried under high vacuum ($10^{-4}/10^{-5}$ mm) at room temperature.

Analysis: Active hydrogen 12.02 mg at/g, Aluminum 6.11 mg at/g, Nitrogen 6.18 mg at/g. $[\alpha]_D^{25} = +30.8°$ (c = 5, benzene).

Reduction of Phosphine Oxides with Chiral Alanes

The following procedure has been used in the reported runs. The required amount of the reducing agent (PIA or DAA) which is calculated from its active hydrogen content determined as before, is dissolved in the solvent (toluene or benzene 1 g/15 ml). The phosphine oxide dissolved in the same solvent (1 g/15 ml) is then added dropwise, the addition rate being adjusted in such a way as to ensure a satisfactory temperature control. The conversion degree is estimated by GLC analysis carried out on samples drawn from the reaction mixture and hydrolised with NaOH/methanol. Finally the reaction is quenched in the same way and the mixture is transferred in a separatory funnel provided with nitrogen inlet and mechanical stirring. A large excess of degassed water is then added in order to remove both the unreacted phosphine oxide and a large part of methanol; the two phases are separated and to the organic layer an equal amount of degassed water is added. Then, by dropwise addition of diluted (1/1) degassed HCl, the pH is adjusted to a intermediate value between the pKa of the optically active amine and the one of the phosphine. The HCl addition is followed by GLC analysis in order to ascertain the total disappearance of the amine from the upper organic layer. The acqueous acidic phase is separated, added with alkali, extracted with ether, the latter dried over sodium sulphate and finally the amine precipitated from it by treatment with gaseous dry HCl. Recovered amine yield ±70% $[\alpha]_D^{25} = -29.9$ (c = 2.5, ethanol).

The organic layer is dried over degassed Na_2SO_4, the solvent removed at reduced pressure and 0°C and the residue distilled under high vacuum to give the pure phosphine (≥ 97% GLC), b.p. 48°C and 40°C for the cyclic and acyclic phosphine respectively (10^{-3} mm). The polarimetric measurements are made on pure undiluted cyclic phosphine and 5% toluene solution of the acyclic one.[4] The acqueous phase containing the phosphine oxide is extracted four times with small amounts of chloroform and the latter dried over sodium sulphate. The compound is isolated by removing the solvent under reduced pressure and recristallized when necessary, from chloroform/n-hexane. Polarimetric analysis of the GLC pure samples are carried out in benzene solution. In the runs carried out in mixed TEA/toluene solution the above procedure has been modified as follows: to the alane dissolved in TEA (1 g/15 ml) the required amount of phosphine oxide dissolved in toluene (1 g/5 ml) is added. After the NaOH/methanol hydrolysis, excess degassed water is added, and a large part of the tertiary amine is removed by distillation at 12 mm and room temperature. The residue, to which toluene is added, is then worked up as previously described.

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