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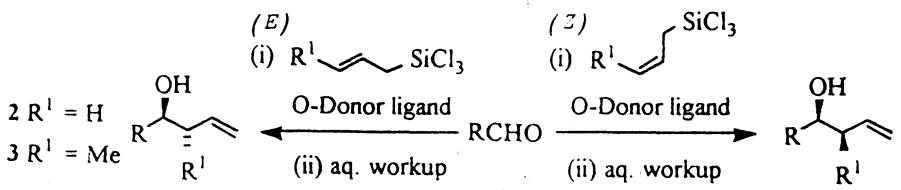
Diastereoselective Synthesis of Chiral Bicyclic Phosphoramides Derived from (S)-2-(Anilinomethyl) Pyrrolidine

H.M. El-HENDAWI, D.J. BERRISFORD†,
R.M. BARAKA* and I.M. El-NAHHAL
Department of Chemistry
Al-Azhar University, Gaza, Palestine

The diastereoselectivity of the chiral bicyclic phosphoramide synthesis can be improved under certain conditions of temperature and degree of polarity of the solvent. Measured diastereomer ratio (exo-isomer : endo-isomer) enhanced from (1.00 : 1.00) to (1.00 : 1.44) in favourable cases. This enhancement in the diastereoselectivity is highly relevant to the development of asymmetric synthesis, where chiral bicyclic phosphoramides are used as catalysts.

INTRODUCTION

Chiral bicyclic phosphoramides have achieved considerable and practical value as ligands in catalysts for asymmetric synthesis, which are usually called O-donor ligands[1–3]. Ligands accelerated or activated catalysis[4] is a recent innovation in the field of asymmetric synthesis. A particular ligand may promote a reaction, which, in the absence of the ligand, is slow, or does not exist. As a consequence, if the ligand L is chiral, stereoselectivity can be imparted on a reaction in which new chiral centres are produced. Previous work at UMIST[1] and elsewhere[5] has shown that the reactions of allyltrichlorosilane with carbonyl compounds to give allylic alcohols occur only in the presence of selected O-donor ligands,[5,6] *e.g.*, L = phosphine oxide (Scheme 1). In contrast, allyltrichlorosilanes are unreactive toward, for example, aldehydes in the absence of a suitable



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Donor ligand = DMF/$(R'_2N)_3P$ = O; R = aryl, alkyl

Scheme-1

*Dr R.M. Baraka: E-mail: alazhar@plant.com.
†Department of Chemistry, UMIST, Faraday Building, Manchester, M60 1QD, UK

O-donor ligand. The reactions are already highly diastereoisomer selective as illustrated, *i.e.*, (E) gives 1 and (Z) gives 2.

Asymmetric allylation of aldehydes using chiral phosphoramide[2, 7, 8] is already established. One of these chiral phosphoramides is the (3R, 7aS)-and (3S, 7aS)-1,2,5,7,7a-hexahydro-2-phenyl-3-piperidinopyrrolo-[1,2-c][1,3,2] diazaphosphole-3-oxide. It has been reported that the R-isomer is more active than the S-isomer as a catalyst for allylation of aldehydes[3]. Our concern in the present work is the enhancement of the relative proportion of the R-isomer.

EXPERIMENTAL

General Experimental Comments

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. ^{31}P NMR spectra were recorded on 200 MHz spectrometer. NMR spectra were recorded in $CDCl_3$ solvent.

Elemental analyses were performed by the UMIST Microanalytical Service Laboratory, U.K.

Infrared spectra were recorded on a Perkin-Elmer 783 IR spectrometer as KBr discs and are reported in cm^{-1}.

Melting points were determined on a Buechi 512 melting point apparatus. Optical rotation values were recorded on an AA 1000 device.

Mass spectra were obtained on a Kratos MS50TC spectrometer and were reported in the form m/z (intensity relative to base = 100). The spectra were normally recorded by the fast atom bombardment method (FAB). High-resolution mass spectra (HRMS) were performed in the Mass Spectrometry, Department of the University of Manchester.

For analytical TLC, 0.25 mm silica gel plates of the type Polygram G/UV_{254} from Machery-Nagel were used and visualization was accomplished by UV light or iodine.

The starting material ((S)-proline) was obtained from Merck and used without further purification.

Flash column chromatography was performed with Merck silica gel 60(230–400 mesh ASTM) with redistilled solvents.

All solvents for reactions were freshly distilled from appropriate drying agents. Triethylamine used had been distilled from CaH_2 and stored over molecular sieves.

Preparation of (3R, 7aS)- and (3S, 7aS)-1,2,5,7,7a-Hexahydro-2-phenyl-3-piperidinopyrrolo-[1,2-c][1,3,2]-diazaphosphole-3-oxide

To a solution of diamine (1 g, 5.67 mmol) and triethylamine (1.146 g, 11.35 mmol) in 7 mL of a dry solvent (different solvents were used) was added piperidino-phosphoric acid-dichloride (2.8 g, 11.35 mmol) in 20 mL of a solvent at the desired temperature under a nitrogen atmosphere. The temperature was maintained as above for 6 h after addition. The solvent was removed *in vacuo* and an ether solution of the residue was filtered. The product was purified by column chromatography on silica (ethyl acetate/hexane, 9 : 1 system).

Analysis:

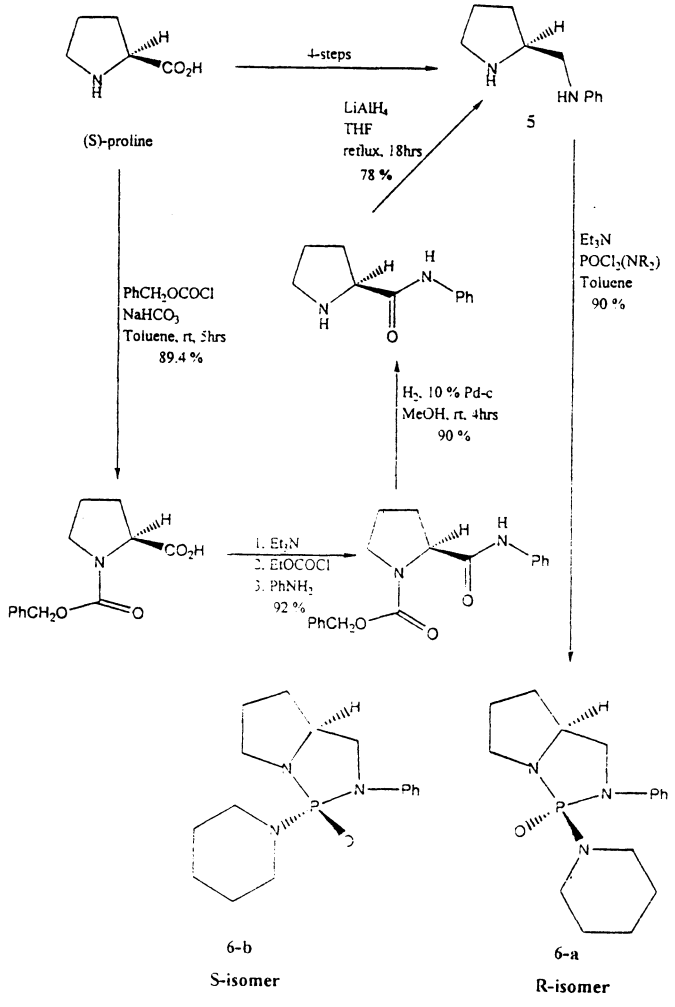
S-isomer: $R_f = 0.32$ (1 : 9, v : v, hexane/ethylacetate); $[\alpha]_D = -23.1°$ (c = 1.15, $CHCl_3$); ^1H NMR δ($CDCl_3$, 300 MHz) 1.24–2.0 (11H, m), 2.84–3 (5H, m), 3.35–3.4 (1H, m), 3.62–3.81 (2H, m), 6.8–6.9 (1H, m), 7.95–7.1 (2H, m), 7.15–7.25 (2H, m); ^{31}P NMR ($CDCl_3$, 200 MHz) 22.5(s); ^{13}C NMR ($CDCl_3$, 300 MHz) 22.6 ($N(CH_2)\underline{C}H_2$, piper. ring), 26 ($NCH_2\underline{C}H_2$, piper ring), 31.5 ($NCH\underline{C}H_2$, pyr. ring), 44.2 ($NCH_2\underline{C}H_2$, pyr. ring), 48.7 ($N\underline{C}H_2$, piper. ring), 57.8 ($N\underline{C}H$, pyr. ring), 102.3($NCH\underline{C}H_2N$), 116.1, 120.6 128.8, 142 (aromatic); MS (FAB) 306($[M + 1]^+$, 96.7), 235(15.7), 221(100), 205(32.8), 173(15.7), 152(13), 130(17), 116(35.5), 106(19.7), 91(31.6), 84(61.8); HRMS calcd. for $C_{16}H_{24}N_3OP$: 305.16926 found: 305.1653; Anal. calcd. for $C_{16}H_{24}N_2PO$: C, 62.93; H, 7.92; N, 13.25; P, 10.14; found: C, 62.8; H, 8.2; N, 13.5; P, 10.0.

R-isomer: $R_f = 0.15$ (1 : 9, v : v, hexane/ethylacetate); $[\alpha]_D = +66.5°$ (c = 1.91, $CHCl_3$); ^1H NMR δ($CDCl_3$, 300 MHz) 1.18–175 (10H, m), 1.93–2.2 (2H, m), 2.9–3.32 (6H, m), 3.65–3.75 (1H, m), 4.0–4.13 (1H, m), 6.8–6.9 (1H, m), 7–7.1 (1H, m), 7.2–7.25 (2H, m); ^{31}P NMR ($CDCl_3$, 200 mHz) 16.9(s); ^{13}C NMR ($CDCl_3$; 300 MHz), 22.6 ($N(CH_2)_2\underline{C}H_2$, piper. ring), 26.2 ($NCH_2\underline{C}H_2$ piper. ring), 27.5 ($NCH\underline{C}H_2$, pyr. ring), 31.6 ($NCH_2\underline{C}H_2$, pyr. ring), 43.9 ($N\underline{C}H_2$, piper. ring), 45.4 ($N\underline{C}H_2$, pyr. ring.), 53($N\underline{C}H$, pyr. ring), 56.4($NCH\underline{C}H_2N$), 115.4, 120.3, 129, 142.8 (aromatic); MS (FAB) 306($[M + 1]^+$, 99), 231(23.6), 221(92.1), 205(19.7), 147(15.8), 130(28), 116(38.8), 106(23.7), 91(28.3), 84(100); HRMS calcd. for $C_{16}H_{24}N_3OP$ 305.16926 found: 305.1653; Anal. calc for $C_{16}H_{24}N_2PO$: C, 62.93; H, 7.92; N, 13.25; P, 10.14; found: C, 62.9; H, 7.9; N, 13.3; P, 10.2.

RESULTS AND DISCUSSION

Phosphoramides were prepared from (S)-proline as shown in Scheme-2. (S)-N-Carboenzyloxyproline was effectively converted to (S)-diamine 5 by using a modified literature procedure[9]. Diamine 5 was treated with piperidino-phosphoric acid-dichloride by using a modified literature procedure[10] to give the R-isomer 6-a and S-isomer 6-b. The relative proportion of each isomer (diastereomer ratio) was determined by ^{31}P NMR (Figs. 1–4)

The reaction of preparation of cyclophosphoramides was carried out under different conditions of temperature and degree of polarity of the solvents (Table 1), in order to enhance the diastereoselectivity; *i.e.*, to increase the relative proportion of one isomer to the other. The reaction was performed in two different solvents, toluene and THF, to assess the effect of solvent. Different temperatures between 0°C and –80°C were also tried to enhance the diastereoselectivity of the reaction (Table 1). It was expected that controlling of the reaction conditions such as the temperature and the polarity of the solvent might have the ability to reach that enhancement. When THF was used as solvent at 0°C, the diastereomer ratio (R-isomer : S-isomer) was 1.15 : 1.00 (Fig. 1 and Table 1), and the chemical yield was 85%. A slightly increasing in the relative proportion of the R-isomer and the chemical yield was obtained, when THF was used as solvent at –80°C, where the diastereomer ratio was 1.20 : 1.00 (Fig. 2), and the chemical yield 88%. Unexpected interchange in the diastereomer ratio was obtained, when the toluene was



Scheme-2

used as solvent at –40°C, where the diastereomer ratio was interchanged from 1.20 : 1.00 to 1.00 : 1.14 (Fig. 3 and Table 1). The diastereomer ratio was interchanged again to the original situation, when the toluene was used as solvent at –80°C, where the diastereomer ratio was interchanged from 1.00 : 1.14 to 1.44 : 1.100 (Fig. 4).

It is found that, in general, nonpolar solvents and low temperatures are necessary for high diastereoselectivity and high yield (Table-1).

The results in Table-1 show a good enhancement in the diastereoselectivity if it is compared with the best literature result, which is 1 : 1[10].

^{31}P NMR spectra show the ratios that are listed in Table-1.

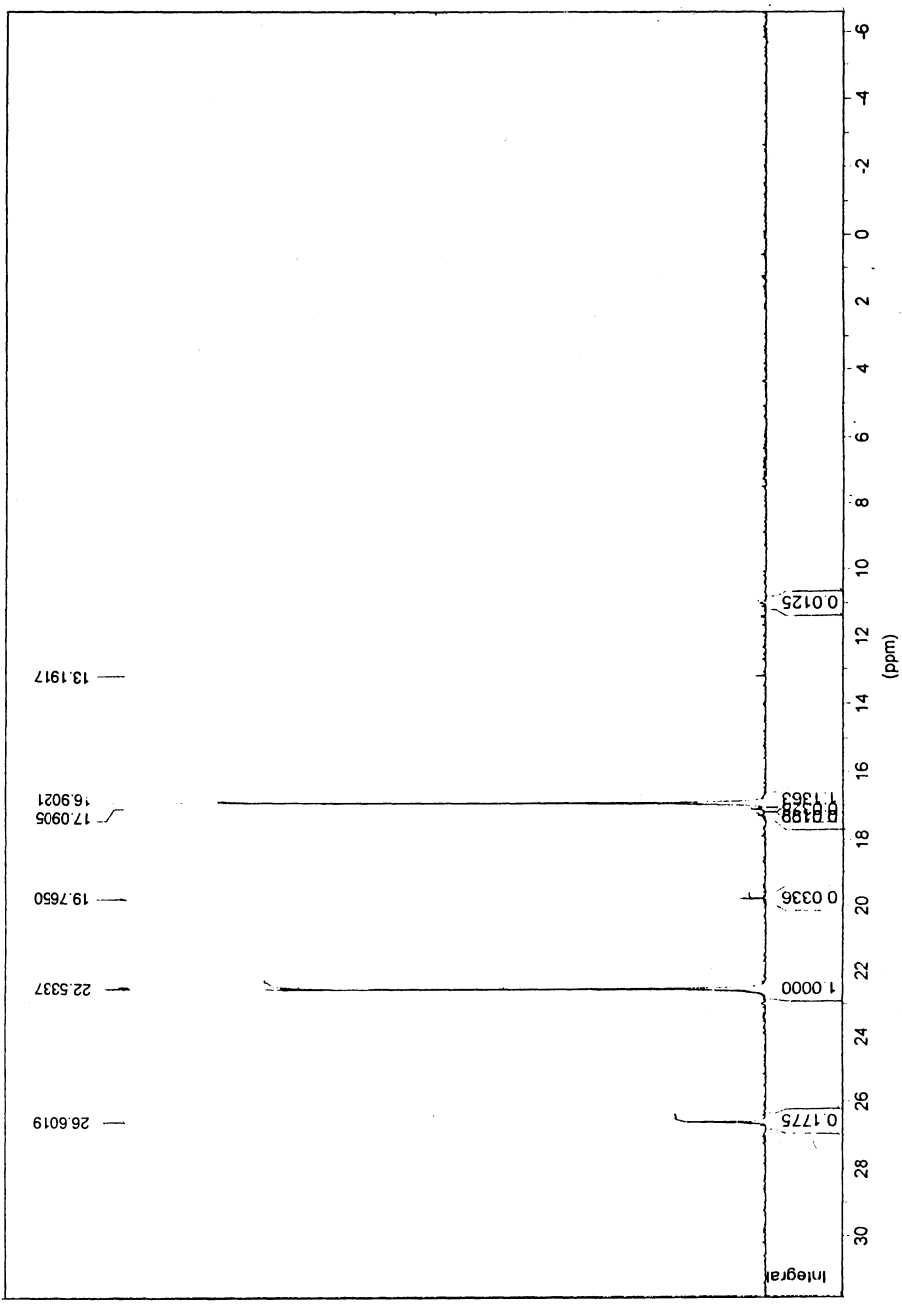


Fig. 1. The ^{31}P NMR spectrum of diastereoisomeric mixture, prepared in THF at 0°C

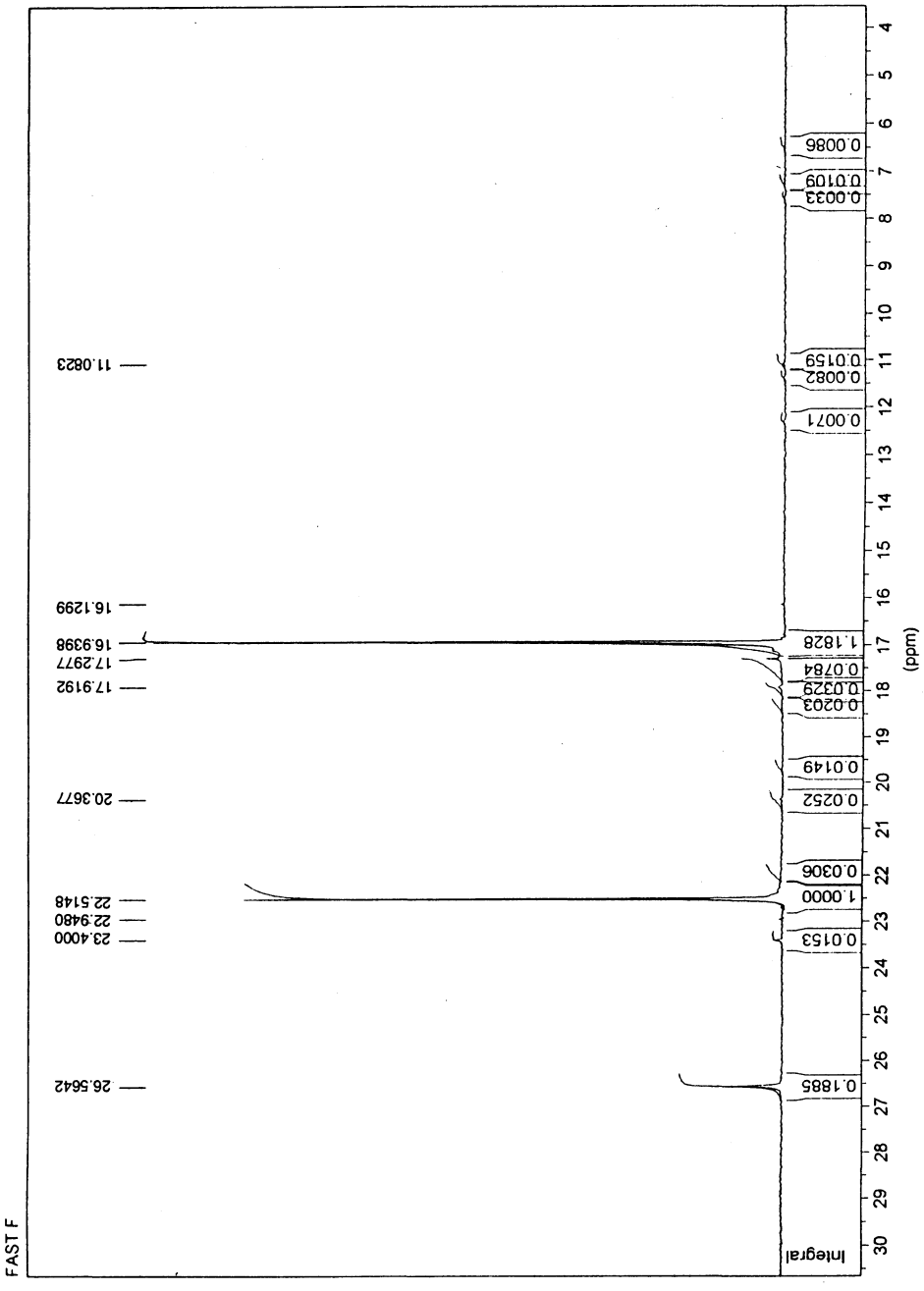


Fig. 2. The ^{31}P NMR spectrum of diastereoisomeric mixture, prepared in THF at –80°C.

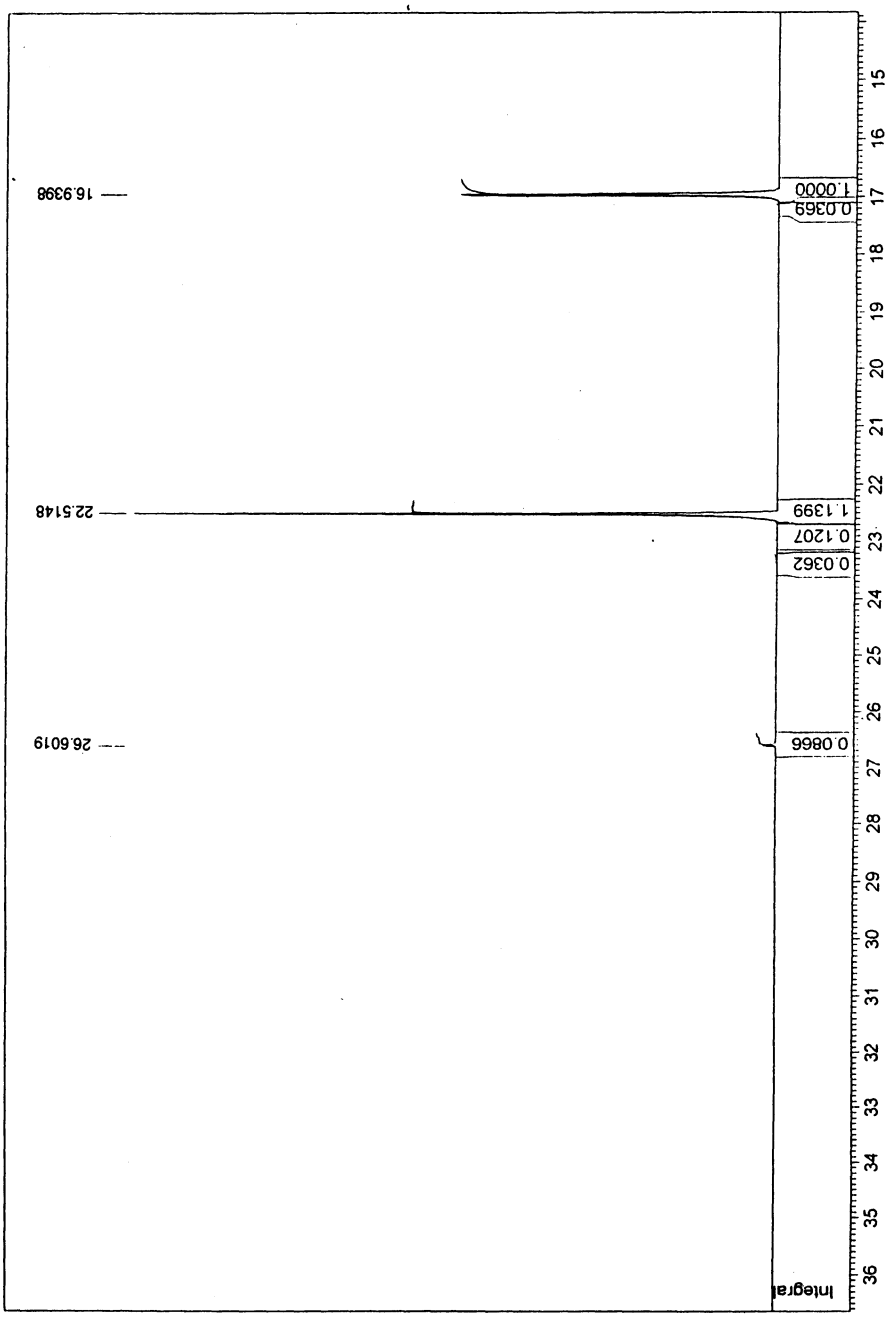


Fig. 3. The ^{31}P NMR spectrum of diastereoisomeric mixture, prepared in toluene at –40°C

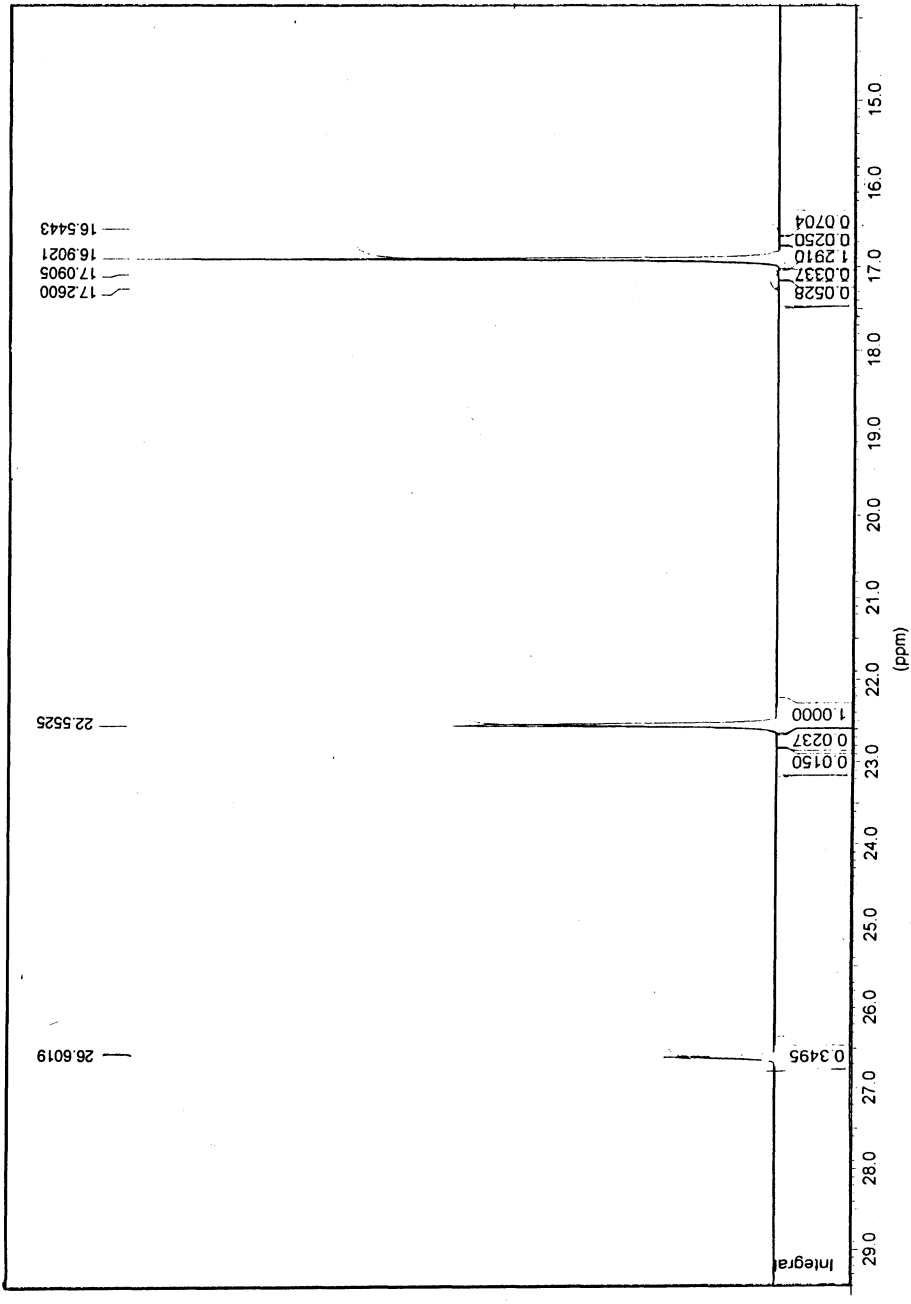


Fig. 4. The ^{31}P NMR spectrum of diastereoisomeric mixture, prepared in toluene at –80°C

TABLE 1.
DIASTEREOSELECTIVITY OBSERVED IN PREPARATION OF CYCLOPHOSPHORAMIDE

Solvent	Temp. (°C)	Diastereoselectivity R-isomer : S-isomer	Chemical yield (%)
THF	0	1.15 : 1.00	85
THF	–80	1.20 : 1.00	88
Toluene	–40	1.00 : 1.14	85
Toluene	–80	1.44 : 1.00	90

The diastereoselectivity was measured by using ^{31}P NMR.
THF = tetrahydrofuran

There were different interchanges in the diastereomer ratios as the conditions were changed. The reason for an isomer to be in a higher yield than the other could be attributed to the stability of the transition state of the isomer. The more stable the diastereoisomeric transition state of the diastereomer under specific conditions the higher the chemical yield. For example, the transition state of the R-isomer is expected to be more stable than that of the S-isomer in THF at 0°C; so the chemical yield of the R-isomer is higher than that of the S-isomer under these conditions of temperature and polarity of solvent.

Conclusion

By controlling of temperature and polarity of the solvent a better result was obtained with the toluene at –80°C, where the diastereomer ratio was 1.44.: 1.00 (R-isomer : S-isomer).

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