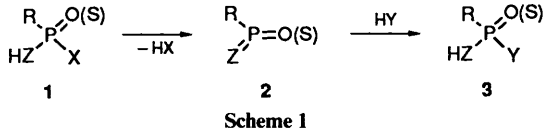
Solvent-dependent Stereoselectivity in the Non-stereospecific Reactions of the Diastereoisomers of a Phosphonamidothioic Chloride with *tert*-Butylamine. A Pointer to the Lifetime of the Thiometaphosphonimidate Intermediate[1]

Martin J. P. Harger
Department of Chemistry, The University, Leicester LE1 7RH, UK

The two diastereoisomers of *N*-[(*S*)-α-phenylethyl]-*P*-*tert*-butylphosphonamidothioic chloride (**9**) give the same mixture of the diastereoisomers of the phosphonamidothioic diamide product (**11**) with Pr^iNH_2 or Bu^tNH_2 in dilute solution, *i.e.* reaction is completely non-stereospecific. The ratio of the diastereoisomers in the product differs significantly from 50:50, *i.e.* reaction is appreciably stereoselective. With Bu^tNH_2 the stereoselectivity increases markedly on going from a solvent of high polarity (MeCN or Me_2CO) to one of low polarity ($CHCl_3$ or cyclohexane), but with Pr^iNH_2 it changes relatively little. In Pr^iNH_2–Bu^tNH_2 competition experiments the $NHPr^i$/$NHBu^t$ product ratio also increases substantially as the polarity of the solvent decreases. These observations are thought to indicate reaction *via* a 3-co-ordinate P^V thiometaphosphonimidate intermediate that exists long enough not only to become liberated, but also, in less polar solvents, to experience unsuccessful collisions with Bu^tNH_2 before being transformed into product.

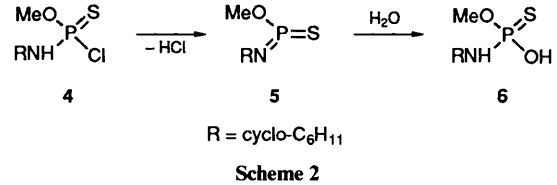
Nucleophilic substitution at a 4-co-ordinate phosphoryl or thiophosphoryl centre usually proceeds by an associative mechanism with a 5-co-ordinate intermediate or transition state.[2,3] If the substrate (**1**; X = leaving group) has a suitable ligand (HZ) attached to the phosphoryl (thiophosphoryl) centre, a dissociative elimination–addition (EA) mechanism is also possible (Scheme 1).[4] This will require the formation of a



Scheme 1

high-energy 3-co-ordinate P^V intermediate **2**. Nonetheless, there is now good evidence that in some situations it can be the preferred route to the product **3** when the ligand HZ is strongly acidic, *i.e.* when Z is oxygen[5] or sulphur.[6,7] Even when Z is nitrogen, the EA mechanism may be competitive if the nucleophile is reasonably basic.[8–10]

Much important information has come from investigations using stereochemistry to probe the existence and lifetime of 3-co-ordinate P^V intermediates in substitution reactions. Recent work has focused mainly on metaphosphate itself,[5] or thiometaphosphate,[6,7] but Gerrard and Hamer's original investigation was concerned with the thiometaphosphorimidate **5** (Scheme 2).[8] They found that optically active samples of the



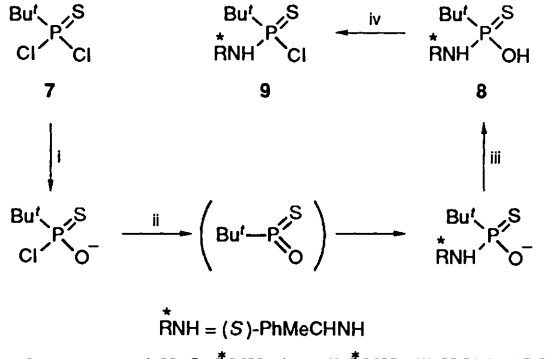
Scheme 2

phosphoramidothioic chloride **4** gave racemic product **6** on alkaline hydrolysis in aqueous dimethoxyethane.[8] The absence of stereospecificity may be seen as evidence that the intermediate **5** not only exists, but lives long enough to become free and symmetrically solvated before reacting with the nucleophile (H_2O) and forming product.

For all its undoubted value as a measure of lifetime, stereospecificity has an inherent limitation. It can take us to the point at which the intermediate exists long enough for substitution to be completely non-stereospecific, but it cannot take us further. With particular reference to 3-co-ordinate P^V species such as **5**, we have therefore explored the possibility of extending the scale of the stereochemical clock, by augmenting measurements of stereospecificity (or the lack of it) with measurements of stereoselectivity. For this we required a substrate related to **4**, but with a chiral alkyl group (α-methylbenzyl) on the N atom to make the faces of the 3-co-ordinate intermediate diastereotopic, rather than enantiotopic. To reduce the risk of competition from associative substitution mechanisms, we also replaced the methoxy group on phosphorus by a bulky *tert*-butyl group.

Results and Discussion

Preparation of the Phosphonamidothioic Chloride **9**.—Attempts to replace selectively just one of the Cl atoms in the phosphonothioic dichloride **7** were unsuccessful. It was therefore subjected to controlled hydrolysis in the presence of an excess of (*S*)-α-methylbenzylamine (5 mol equiv.) to give the phosphonamidothioic acid **8** (Scheme 3). Reaction was very



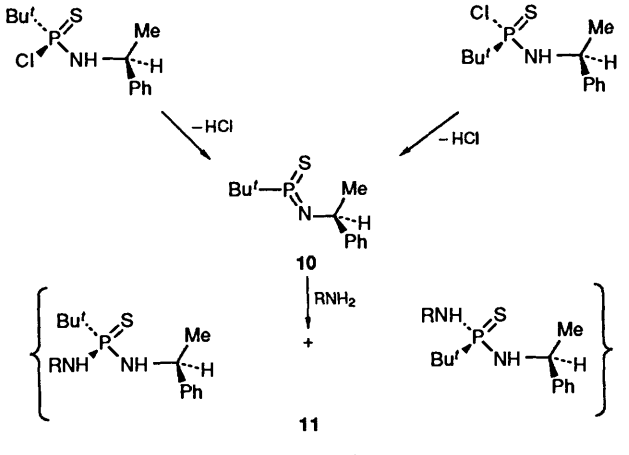
Scheme 3 *Reagents:* i, H_2O–$\overset{*}{R}NH_2$, heat; ii, $\overset{*}{R}NH_2$; iii, HCl; iv, $(COCl)_2$

slow (some unchanged starting material remained after 25 h at 75–80 °C), and gave substantial amounts of the expected by-products $Bu^tP(S)(OH)_2$ and $Bu^tP(S)(NH\overset{*}{R})_2$, but the phosphonamidothioic acid was easily isolated and purified. Not

surprisingly, it was obtained as an approximately 1:1 mixture of diastereoisomers (δ_P 93.4 and 95.0 ppm). With oxalyl chloride it was readily converted into the required phosphonamidothoic chloride **9**. Attempts to separate the diasteroisomers of the acid **8** by fractional crystallisation of the original 1:1 mixture met with little success, but hydrolysis of the chloride gave back a 2:1 mixture from which a pure sample of one diastereoisomer of the acid (δ_P 95.0 ppm) could be isolated. This, however, did not react stereospecifically with oxalyl chloride. It was therefore necessary to resort to chromatography of the phosphonamidothioic chloride. The diastereoisomers were only poorly separated, but two useful samples were eventually obtained: an oil A, 94.5% fast-running diasteroisomer, t_R 13.0 min (OV 101 capillary at 185 °C), $\delta_H(CCl_4)$ 1.62 (d, J_{HH} = 6.5 Hz, Me) and 1.29 (d, J_{PH} = 21 Hz, Bu^t); and a solid B, 89% slow-running diastereoisomer, t_R 13.3 min, $\delta_H(CCl_4)$ 1.51 (d, J_{HH} = 6.5 Hz, Me) and 1.30 (d, J_{PH} = 21 Hz, Bu^t).

Stereospecificity with tert-*Butylamine*.—The two diastereoisomerically enriched samples (A and B) of the phosphonamidothioic chloride **9** were separately treated with *tert*-butylamine (10–20 mol equiv.) at various dilutions in MeCN (T = *ca.* 25 °C). Reaction was rapid even at the lowest concentration of amine (0.25 mol dm^{-3}), and was complete within 1 min. The product in every case was seen by GLC (3% OV 225 at 192 °C) to be a mixture of the diastereoisomers of the amide **11** (R = Bu^t) (Scheme 4), the one with the shorter retention time (t_R = 14.3 min) (^{1}H NMR; lowfield P*Bu*^{t}; highfield N*Bu*^{t} and NC*HMe*Ph) being always in excess of the other (t_R = 16.7 min).

At the lowest amine concentration (0.25 mol dm^{-3}) the two samples of substrate gave amide having exactly the same 57:43 ratio of diastereoisomers. Control experiments [using a sample of **11** (R = Bu^t) with an 80:20 disastereoisomer ratio] showed the product to be configurationally stable in MeCN containing Bu^{t}NH$_2$ and Bu^{t}NH$_3$Cl, even over an extended period. For the substrate, however, the situation was less clear cut. In reactions halted at *ca.* 50% completion (t = 6 s; quenched with CF_3CO_2H) the remaining substrate was seen to be essentially unchanged in the case of B (89% one diastereoisomer by GLC), but of slightly reduced diastereoisomeric purity in the case of A (90%, from 94.5%). The products were still identical mixtures of diastereoisomers. Even if there is some 'racemisation' of the substrate during reaction (the change observed may actually result from the minor component of A reacting relatively slowly), its influence on the stereochemistry of the product at the time of quenching must have been negligible. There seems no doubt that with 0.25 mol dm^{-3} Bu^{t}NH$_2$ the substitution reaction is truly devoid of all stereospecificity. That being so, it must proceed entirely *via* the free thiometaphosphonimidate **10**.



Scheme 4

Table 1 Reactions of substrate **9** (samples A and B) with Bu^{t}NH$_2$ in MeCN: ratio of diastereoisomers in the product (**11**; R = Bu^t)[a]

	Product diastereoisomer ratio[b]	
[Bu^{t}NH$_2$]/mol dm^{-3}	Sample A	Sample B
0.25	57:43	57:43
1.0	59:41	57:43
2.0	59.5:40.5	57:43
4.0	61.5:38.5	57:43
8.0	61:5:38.5	59:41
Neat	68:32	60.5:39.5

[a] GLC analysis; 3% OV 225 at 192 °C; t_R = 14.3 (major) and 16.7 min. [b] Estimated uncertainty ±0.5% in each diastereoisomer (assuming same detector response for both diastereoisomers).

At higher amine concentrations the two diastereoisomers of the phosphonamidothioic chloride no longer form identical products (Table 1). The divergence in behaviour is small, but mechanistically significant in as much as it shows that reaction no longer proceeds entirely *via* the free thiometaphosphonimidate.* As to the nature of the competing process, it cannot be simply associative; thiophosphoryl compounds are less reactive than their P=O analogues in normal associative substitution,[11] but with *tert*-butylamine the P=S substrate **9** ($t_{\frac{1}{2}}$ ~ 6 s with 0.25 mol dm^{-3} amine) is very much more reactive than its P=O counterpart **12** ($t_{\frac{1}{2}}$ 10^4 s with 0.5 mol dm^{-3} amine). Instead, it seems likely that a preassociation EA mechanism[12] begins to compete with simple EA. In the preassociation mechanism the nucleophile will already be present when the leaving group departs, so the thiometaphosphonimidate will not become entirely free. The precise stereochemistry is difficult to predict,[9,10] but some bias towards inversion of configuration would hardly be surprising.

Stereoselectivity with tert-*Butylamine*.—For the completely non-stereospecific reaction of the phosphonamidothioic chloride **9** with 0.25 mol dm^{-3} Bu^{t}NH$_2$, the unequal yields of the two diastereoisomers of product implies some stereoselectivity (57:43) in the reaction of the free thiometaphosphonimidate, *i.e.* one of the diastereotopic faces of **10** reacts more readily than the other. At higher amine concentrations the stereoselectivity of the free intermediate seems if anything slightly greater (*e.g.* 60:40 with 8 mol dm^{-3} Bu^{t}NH$_2$), but it is difficult to separate with confidence the influence of the (slight) stereospecificity of the competing preassociation mechanism. In examining the influence of the solvent on stereoselectivity we have therefore kept to low concentrations of amine, hoping to avoid the uncertainties that any stereospecificity might introduce.

Many otherwise attractive solvents could not be included because of their potential to divert the thiometaphosphonimidate to other products (MeOH, EtOH), or distort the stereochemistry of product formation by acting as nucleophilic catalysts (DMF, DMSO). Nonetheless, by moving from MeCN to Me_2CO, CH_2Cl_2, $CHCl_3$, and cyclohexane it was possible to

* Our results (Table 1) somewhat understate the divergence in behaviour between the two diastereoisomers. Knowing the diastereoisomer composition of our substrate samples (A, 94.5:5.5; B, 11:89) it is easy to deduce the true behaviour of the single diastereoisomers. Even in the most extreme case (neat Bu^{t}NH$_2$), however, the picture changes little (deduced, 68.5:31.5 and 59.5:40.5; observed, 68:32 and 60.5:39.5). In any case, it is those situations in which the behaviour of the diastereoisomers is identical (reactions totally non-stereospecific) that are of particular interest in the present work, and where there is no divergence in behaviour, there is no understatement.

Table 2 Reactions of substrate **9** (samples A and B) with Bu^tNH_2 (0.25 mol dm^{-3}) in different solvents. Ratio of diastereoisomers in the product (**11**; R = Bu^t).[a]

Solvent	(ε_r)	Product diastereoisomer ratio[b] Sample A	Sample B
MeCN	(35.9)	57:43	57:43
Me_2CO	(20.6)	58.5:41.5	58.5:41.5
CH_2Cl_2	(8.9)	63:37	63:37
$CHCl_3$	(4.8)	78:22	78:22
cyclo-C_6H_{12}	(2.0)	80:20	81:19

[a,b] See footnotes to Table 1.

Table 3 Reactions of substrate **9** (samples A and B) with Pr^iNH_2 (0.25 mol dm^{-3}) in different solvents. Ratio of diastereoisomers in the product (**11**; R = Pr^i).[a]

Solvent	Product diastereoisomer ratio[b] Sample A	Sample B
MeCN	54.5:45.5	53.5:46.5
Me_2CO	54:46	54:46
CH_2Cl_2	54.5:45.5	54.5:45.5
$CHCl_3$	57.5:42.5	57.5:42.5
cyclo-C_6H_{12}	64.5:35.5	62:38

[a] GLC analysis; 3% OV 225 at 198 °C; t_R = 10.3 (major) and 12.6 min. [b] See footnote *b* to Table 1.

Table 4 Reaction of substrate **9** (mixture of diastereoisomers) with 1:1 Pr^iNH_2–Bu^tNH_2 (0.25 mol dm^{-3}; 20 mol equiv.) in different solvents. Ratio of product GLC peak areas.[a]

Solvent	$NHPr^i/NHBu^t$
MeCN	1.65
Me_2CO	1.6
CH_2Cl_2	7.7
$CHCl_3$	9.5
cyclo-C_6H_{12}	12.5

[a] GLC analysis; OV 101 capillary at 205 °C; t_R/min 16.7 and 17.9 ($NHPr^i$), 19.4 and 20.5 ($NHBu^t$). Peak areas not corrected for any possible difference in detector response for **11** (R = Pr^i) and **11** (R = Bu^t).

cover a reasonable range of solvent character. The products obtained from the two diastereoisomerically enriched samples (A and B) of the substrate with 0.25 mol dm^{-3} *tert*-butylamine in each of the solvents were indistinguishable, or practically so. As with MeCN substitution is therefore completely free of stereospecificity. Between the various solvents, however, there were quite pronounced differences (Table 2). In particular, the rather small stereoselectivity seen in MeCN and Me_2CO increased appreciably in the less polar CH_2Cl_2, and markedly in the relatively non-polar $CHCl_3$ and cyclohexane.

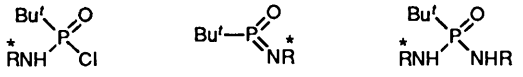
Stereoselectivity of itself does not necessarily require the thiometaphosphonimidate to survive collisions with the nucleophile, since one of its diastereotopic faces may be intrinsically more accessible than the other. However, so long as the relative accessibility of the faces remains more or less unchanged, as seems likely with the solvents we have examined, a *change* in stereoselectivity does require that some previously successful collisions should fail to go to product. The extent of the change will then be determined by the proportion of the collisions at each face of the thiometaphosphonimidate that no longer succeed in forming product. If lack of success were confined to just one face, the observed increase in stereoselectivity, from 57:43 to 80:20 (*i.e.* 57:14), would imply that only one in three of the potentially successful collisions at the less reactive face form product in cyclohexane. In reality it seems more likely that both faces experience some unsuccessful collisions, and that the stereoselectivity changes because one of the faces suffers more than the other. Either way, the essential point is that the thiometaphosphonimidate seems able to survive potentially successful collisions with Bu^tNH_2, at least in less polar solvents.*

Stereochemistry with Isopropylamine.—Isopropylamine is a more reactive (less hindered) nucleophile than *tert*-butylamine, and potentially successful collisions with the thiometaphophonimidate should not be so likely to fail. Any increase in stereoselectivity on moving to solvents of lower polarity should in consequence be relatively small. The diastereoisomerically enriched samples (A and B) of the phosphonamidothioic chloride **9** were therefore treated with isopropylamine (0.25 mol dm^{-3}) in the same solvents as were used for *tert*-butylamine. The results are shown in Table 3. In all solvents reaction is completely non-stereospecific (liberated intermediate), or very nearly so, and the thiometaphosphonimidate displays some stereoselectivity in product formation. The stereoselectivity is less than with *tert*-butylamine, however. More important, the stereoselectivity does indeed increase only comparatively little, on going to solvents of lower polarity.

Competition between Isopropylamine and tert-*Butylamine.*—If it is true that reduced solvent polarity causes unsuccessful collisions between the thiometaphosphonimidate and the nucleophile to increase substantially in the case of Bu^tNH_2, but only slightly in the case of Pr^iNH_2, it should also enhance the discrimination between competing Pr^iNH_2 and Bu^tNH_2. Using the same range of solvents as before, the phosphonamidothioic chloride **9** (mixture of diastereoisomers) was treated with an equimolar mixture of Pr^iNH_2 and Bu^tNH_2 (20 mol equiv.; 0.25 mol dm^{-3}), and the $NHPr^i/NHBu^t$ product ratio [**11** (R = Pr^i): **11** (R = Bu^t)] was determined by GLC (Table 4). Although in detail the correlation is not perfect, in essence the pattern is clear: the discrimination against Bu^tNH_2 is greater in solvents of lower polarity, just as the stereoselectivity of the reaction with Bu^tNH_2 is greater too. Had the reactions not been shown to be free of stereospecficity, it might have been tempting to attribute the increased discrimination against Bu^tNH_2 to a different cause, *viz.* increased competition from an associative substitution mechanism. For this, reaction with the less hindered Pr^iNH_2 would certainly be much preferred,[9,13] but stereospecificity would not be absent.[9] In general, one cannot expect competition experiments alone to report on the lifetime of a reactive intermediate with the same authority as a stereochemical study. Moreover, with competition experiments there is always the danger that preferential solvation of the substrate by one of the nucleophiles will unfairly favour one of the products,[14] whereas with stereoselectivity the two products (diastereoisomers) are both derived from the same nucleophile.

* The solvents we have used differ in many respects. For convenience we have chosen to relate the changes in stereoselectivity to polarity, and to use relative permittivity (ε_r; Table 2) as a measure of polarity. Other characteristics of the solvent may well be at least as important [M. Chastrette, M. Rajzmann, M. Chanon and K. F. Purcell, *J. Am. Chem. Soc.*, 1985, **107**, 1; M. H. Abraham, P. L. Grellier, J-L. M. Abboud, R. M. Doherty and R. W. Taft, *Can. J. Chem.*, 1988, **66**, 2673]. Our only real concern at present is the fact that different solvents give rise to substantially different stereoselectivities. (Notwithstanding, the relative lack of success of collisions between the thiometaphosphonimidate and the nucleophile in solvents of low polarity might suggest that the transition state for product formation is more polar in character than the species from which it is formed).

Comparative Behaviour of the P=O *Substrate.*—Previous work has shown that the P=O compound **12** also reacts dissociatively with amines, although reaction is very slow compared with the P=S substrate ($k_{P=O}/k_{P=S} < 10^{-3}$), and the EA mechanism seems to depend more on preassociation. Such differences may reflect a lesser stability of the metaphosphonimidate intermediate **13**, relative to its P=S counterpart **10**, and it would not be surprising to find it less able to survive collisions with a nucleophile. The influence of the



12 **13** **14**

*RNH = (*S*)-PhMeCHNH

solvent on the reaction of the P=O substrate **12** (mixture of diastereoisomers) with Pr^iNH_2–Bu^tNH_2 was therefore briefly examined. Meaningful results could not be obtained in Me_2CO (Pr^iNH_2 reacted with the solvent more quickly than the substrate underwent substitution) but in the other solvents (MeCN, CH_2Cl_2, $CHCl_3$, cyclohexane) it was seen (GLC) that the $NHPr^i/NHBu^t$ product ratio increased only marginally in going from MeCN to cyclohexane ($\leqslant 1.5$ in all solvents), and that for both of the products the ratio of the diastereoisomers increased little (cyclohexane) or not at all (CH_2Cl_2, $CHCl_3$). The contrast with the P=S substrate is unmistakable.

Conclusions

By working with diastereoisomers rather than enantiomers it is possible to examine stereoselectivity as well as stereospecificity. In the particular case of the phosphonamidothioic chloride **9**, the complete lack of stereospecificity in the reactions with amines at low concentrations shows that the thiometaphosphonimidate intermediate **10** not only exists, but lives long enough to diffuse away from the leaving group and become fully liberated before it is captured by the nucleophile. Stereoselectivity then takes us further. The increase in the stereoselectivity of the reaction with *tert*-butylamine in solvents of lower polarity shows that the lifetime of the thiometaphosphonimidate is sufficient not only for it to become fully liberated, but also to make some unsuccessful collisions with the nucleophile before finally being transformed into product.

Experimental

Instrumentation was as previously described.[10] GLC analyses were performed with a 25 m × 0.25 mm i.d. fused silica capillary column containing a 0.25 μm film of OV 101 (He carrier gas; split injection) or a 1.5 m × 4 mm i.d. glass column packed with 3% OV 225 coated on silanised 100–120 mesh diatomite C 'Q' (N_2 carrier gas; on-column injection). Amines were dried over and distilled from KOH. Acetonitrile and dichloromethane were distilled from calcium hydride. Cyclohexane was dried over sodium wire, and acetone over calcium sulphate. Chloroform was passed through a column of alumina immediately prior to use. Light petroleum refers to the fraction b.p. 60–80 °C unless otherwise indicated. *tert*-Butylphosphonothioic dichloride (**7**) was obtained by a literature method,[15] the product obtained by sublimation being crystallised from MeOH–H_2O (20:1) to remove some remaining $Bu^tP(O)Cl_2$.

N-[(S)-α-*Phenylethyl*]-P-*t-butylphosphonamidothioic Acid* (**8**).—A mixture of *tert*-butylphosphonothioic dichloride (1.38 g, 7.2 mmol) and (*S*)-α-phenylethylamine (4.36 g, 36 mmol) was stirred (strong magnet) and heated (bath temp. 75–80 °C) with water (0.13 g, 7.2 mmol). Additional water (8.6 mmol) was added in six equal portions at hourly intervals, and a further portion (1.4 mmol) at $t = 23$ h. The substrate was >90% consumed (^{31}P NMR spectroscopy) by $t = 25$ h. The reaction mixture was diluted with chloroform and extracted with 1 mol dm^{-3} sodium hydroxide solution (26 cm^3). The aqueous extract was carefully acidified (conc. HCl; just sufficient to make it strongly acidic) and immediately extracted with chloroform. Evaporation of the solvent (no heat) afforded N-[(S)-α-*phenylethyl*]-P-tert-*butylphosphonamidothioic acid* (**8**) (0.71 g, 38%) as a mixture of diastereoisomers (*ca.* 1:1), m.p. 94–97 °C (from CH_2Cl_2–light petroleum); ν_{max}(Nujol)/cm^{-1} 3410 and 3340 (NH); $\delta_P(CDCl_3)$ 95.0 and 93.4; $\delta_H(CDCl_3)$ 7.4–7.1 (5 H, m), 5.8–4.4 (br, 2 H, OH and NH), 4.78 and 4.70 (1 H, both dq, $J_{PH} = 11$, $J_{HH} = 7$ Hz), 1.53 and 1.48 (3 H, both d, $J_{HH} = 7$ Hz) and 1.17 and 1.12 (9 H, both d, $J_{PH} = 18$ Hz) (Found: C, 56.1; H, 7.9; N, 5.3. $C_{12}H_{20}NOPS$ requires C, 56.0; H, 7.8; N, 5.4%). A by-product [δ_P 97.4; probably $Bu^tP(S)(OH)_2$] remained in the aqueous portion. The original chloroform portion afforded unchanged substrate and N,N′-*bis*[(S)-α-*phenylethyl*]-P-tert-*butylphosphonothioic diamide* (0.52 g, 20%), m.p. 90.5–91.5 °C (from ether–light petroleum); *m/z* 360 (M^+, 4%), 120 (100) and 105 (60); ν_{max}(Nujol)/cm^{-1} 3410 and 3280 (NH); $\delta_P(CDCl_3)$ 86.9; $\delta_H(CDCl_3)$ 7.4–6.9 (10 H, m), 4.9–4.3 (2 H, m), 2.31 (br, 1 H, NH), 1.96 (br, 1 H, NH), 1.47 (3 H, d, $J_{HH} = 7$ Hz), 1.04 (9 H, d, $J_{PH} = 17$ Hz) and 1.03 (3 H, d, $J_{HH} = 7$ Hz) (Found: C, 67.2; H, 8.2; N, 7.7. $C_{20}H_{29}N_2PS$ requires C, 66.6; H, 8.1; N, 7.8%).

The 1:1 diastereoisomer mixture of the acid **8** was transformed into a 2:1 mixture by conversion into the acid chloride **9** (see below) and hydrolysis (2 mol dm^{-3} NaOH) back to the acid. Fractional crystallisation of this 2:1 mixture from chloroform–light petroleum afforded a pure sample of a single diastereoisomer (10%), $\delta_P(CH_2Cl_2)$ 95.0; $\delta_H(CDCl_3)$ 4.78 (1 H, dq, $J_{PH} = 11$, $J_{HH} = 7$ Hz), 1.53 (3 H, d, $J_{HH} = 7$ Hz) and 1.12 (9 H, d, $J_{PH} = 18$ Hz).

N-[(S)-α-*Phenylethyl*]-P-tert-*butylphosphonamidothioic Chloride* (**9**).—A solution of the phosphonamidothioic acid **8** (0.71 g, 2.76 mmol) in ether (10 cm^3) was stirred and cooled (ice) while oxalyl chloride (0.70 g, 5.5 mmol) was added in portions. After 1.2 h at room temperature, volatile material was evaporated to give the phosphonamidothioic chloride **9** as a mixture of diastereoisomers (t_R = 13.0 and 13.3 min; OV 101 capillary at 185 °C) (not resolved by TLC). Portions (*ca.* 200 mg) of the mixture were flash chromatographed on a column of silica (60 μm; 26 × 2 cm). Elution with light petroleum containing ethyl acetate (1–1.5%) gave some early and late fractions substantially enriched (≥80%) in the individual diastereoisomers. Attempted crystallisation (light petroleum) of the early fractions gave crystals of reduced diastereoisomeric purity and, from the mother liquor, an oil A: 94.5% one diastereoisomer (t_R = 13.0 min) of **9**: $\delta_H(CCl_4$; 300 MHz) 7.3–7.15 (5 H, m), 5.06 (1 H, ddq, $J_{PH} = 11$, $J_{HH} = 9.5$, 6.5 Hz), 3.10 (br, 1 H, m, NH), 1.62 (3 H, d, $J_{HH} = 6.5$ Hz) and 1.29 (9 H, d, $J_{PH} = 21$ Hz). Crystallisation (light petroleum) of the late fractions gave a solid B; 89% one diastereoisomer (t_R = 13.3 min) of **9**: $\delta_H(CCl_4$; 300 MHz) 7.35–7.15 (5 H, m), 4.93 (1 H, ddq, $J_{PH} = 13$, $J_{HH} = 9$, 6.5 Hz), 3.27 (br, 1 H, m, NH), 1.51 (3 H, d, $J_{HH} = 6.5$ Hz) and 1.30 (9 H, d, $J_{PH} = 21$ Hz); further crystallisation did not increase the diastereoisomeric purity. Crystallisation of some intermediate fractions gave a 1:2 mixture of the diastereoisomers (t_R = 13.3 in excess) of **9**: m.p. 62–65 °C; *m/z* 277, 275 (M^+, 20%), 244, 242 ($M^+ - SH$, 50), 220, 218 ($M^+ - C_4H_9$, 30), 120 (100) and 105 (80); ν_{max}(Nujol)/cm^{-1} 3320 (NH); $\delta_P(CDCl_3)$ 109.3 (both di-

astereoisomers) (Found: C, 52.4; H, 6.95; N, 4.9. $C_{12}H_{19}ClNPS$ requires C, 52.3; H, 6.9; N, 5.1%).

N-[(S)-α-*Phenylethyl*]-N′,P-*di*-tert-*butylphosphonothioic Diamide* (**11**; R = Bu^t).—The phosphonamidothioic chloride (**9**) (55 mg, 0.2 mmol) was added to *tert*-butylamine (88 mg, 1.2 mmol) in dichloromethane (2 cm^3). After 10 min, volatile material was evaporated off and the residue was partitioned between chloroform and water. The organic layer was separated, dried and concentrated to give the diamide **11** (R = Bu^t) as an unequal mixture of diastereoisomers (values for major diastereoisomer italicised); t_R = *14.3* and 16.7 min (3% OV 225 at 192 °C); $\delta_P(CDCl_3)$ 78.1 and *78.0*; $\delta_H(CDCl_3$; 300 MHz) 7.35–7.15 (5 H, m), 4.79 and *4.69* (1 H; both ddq, J_{PH} = 12, J_{HH} = 9.5 or *8*, and 7 Hz), 2.38 (1 H, m, NH), 1.98 and *1.81* (1 H; both br d, J_{PH} ~ 8 Hz, NH), 1.49 and *1.47* (3 H, both d, J_{HH} = 7 Hz), 1.41 and *1.21* (9 H, both s, NBu^t) and *1.17* and 0.99 (9 H, both d, J_{PH} = 17 Hz, PBu^t). After purification by sublimation (60 °C at 0.2 mmHg), m.p. 69–77 °C; *m/z* 312 (M$^+$, 7%), 120 (100) and 105 (50); ν_{max}(Nujol)/cm^{-1} 3330 (NH) (Found: C, 61.2; H, 9.3; N, 8.9. $C_{16}H_{29}N_2PS$ requires C, 61.5; H, 9.35; N, 9.0%).

N-*Isopropyl*-N′-[(S)-α-*phenylethyl*]-P-tert-*butylphosphonothioic Diamide* (**11**; R = Pr^i).—The phosphonamidothioic chloride **9** and isopropylamine gave (as above) the diamide **9** (R = Pr^i) as an unequal mixture of diastereoisomers (values for major diastereoisomer italicised): t_R *10.3* and 12.6 min (3% OV 225 at 198 °C); $\delta_P(CDCl_3)$ *84.9* and 84.1; $\delta_H(CDCl_3$; 90 MHz) 7.35–7.05 (5 H, m), 4.65 (1 H, m), 3.51 (1 H, m, CH of NPr^i), 2.3 (br, 1 H, NH), 1.85 (br, 1 H, NH) 1.47 and *1.46* (3 H, both d, J_{HH} = 7 Hz), 1.18 and 1.08 (9 H, both d, J_{PH} = 17 Hz, PBu^t), 1.17 and *0.93* (3 H, both d, J_{HH} = 6 Hz, CH_3 of NPr^i) and 1.10 and *0.86* (3 H, both d, J_{HH} = 6 Hz, CH_3 of NPr^i). Purified by crystallisation from light petroleum (b.p. 40–60 °C), m.p. 49–50 °C; *m/z* 298 (M$^+$, 12%), 120 (100) and 105 (60); ν_{max}(Nujol)/cm^{-1} 3415, 3375 and 3295 (NH) (Found: C, 60.2; H, 9.1; N, 9.1. $C_{15}H_{27}N_2PS$ requires C, 60.4; H, 9.1; N, 9.4%).

Stereochemical Studies.—*tert*-Butylamine (10 mol equiv. generally; 20 mol equiv. for 8.0 mol dm^{-3} and neat reactions) was added to the diastereoisomerically enriched phosphonamidothioic chloride **9** (sample A or B) (3–6 μmol) dissolved in MeCN to give a reaction mixture *ca.* 0.25, 1.0, 2.0, 4.0 or 8.0 mol dm^{-3} in amine. Reactions were also carried out in acetone, CH_2Cl_2, $CHCl_3$ and cyclohexane (0.25 mol dm^{-3} Bu^{t}NH$_2$ only) and in neat amine. With isopropylamine the same solvents were employed (0.25 mol dm^{-3} Pr^{i}NH$_2$ only). The reaction mixtures were maintained at *ca.* 25 °C for 5 min. Volatile material was evaporated off and the residue, dissolved in CH_2Cl_2, was examined by GLC (see Tables 1–3).

Stereochemical Controls.—(*a*) A sample of the phosphonothioic diamide **11** (R = Bu^t) having a 4:1 diastereoisomer ratio was dissolved in MeCN containing Bu^{t}NH$_3$Cl or a mixture of Bu^{t}NH$_2$ and Bu^{t}NH$_3$Cl. No change in the diastereoisomer ratio was apparent (GLC) after ⩾5 h at 25 °C.

(*b*) Reaction of the phosphonamidothioic chloride **9** (sample A or B) with 0.25 mol dm^{-3} Bu^{t}NH$_2$ in MeCN at 25 °C was quenched after 6 s by addition of CF_3CO_2H (slight excess). GLC analysis (OV 101 capillary at 185 °C) showed comparable amounts of unchanged substrate **9** and product **11** (R = Bu^t). The ratio of diastereoisomers in the substrate (t_R = 13.0 and 13.3 min) was 9:1 (sample A) or 1:8 (sample B), and in the product (t_R = 19.8 and 21.2 min) was 1.3:1 (samples A and B).

Competition Experiments.—The phosphonamidothioic chloride **9** (mixture of diastereoisomers) was added to an equimolar mixture of Pr^{i}NH$_2$ and Bu^{t}NH$_2$ (20 mol equiv.) dissolved in MeCN, acetone, CH_2Cl_2, $CHCl_3$ or cyclohexane (0.25 mol dm^{-3} total amine) at *ca.* 25 °C. After ⩾5 min the product was analysed by GLC (see Table 4).

Similar experiments were carried out using the phosphonamidic chloride **12** (mixture of diastereoisomers).[10] Because these reactions were much slower, the reaction mixtures were contained in sealed tubes. After 50 h the mixtures were examined by GLC (OV 101 capillary at 207 °C). In every case some unchanged substrate (t_R = 6.35 and 6.5 min) (7–85%) was still present. The products **14** (R = Pr^i) (t_R = 8.1 and 8.6 min)[10] and **14** (R = Bu^t) (t_R = 8.8 and 9.2 min)[10] were not sufficiently well separated for precise analysis, but a reasonable comparison could be made of the results for MeCN (for which accurate data was already available[10]) and the other solvents. Compared with MeCN the NHPr^i:NHBu^t product ratio was the same (CH_2Cl_2) or slightly larger [$CHCl_3$ (×1.1), cyclohexane (×1.2)], and the diastereoisomer ratio for both of the products was the same (±0.8%; acetone, CH_2Cl_2, $CHCl_3$) or slightly larger (cyclohexane). In acetone there was very little of the NHPr^i product, presumably because Pr^{i}NH$_2$ reacted with the solvent, and in this case the diastereoisomer ratio above relates to the NHBu^t product only.

References

1 Preliminary communication, M. J. P. Harger, *J. Chem. Soc., Chem. Commun.*, 1988, 1256.
2 R. S. McDowell and A. Streitwieser, *J. Am. Chem. Soc.*, 1985, **107**, 5849 and references cited therein; M. A. Waring and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1989, 1742.
3 G. R. J. Thatcher and R. Kluger, *Adv. Phys. Org. Chem.*, 1989, **25**, 99.
4 F. H. Westheimer, *Chem. Rev.*, 1981, **81**, 313; M. Regitz and G. Maas, *Top. Curr. Chem.*, 1981, **97**, 71.
5 J. M. Friedman, S. Freeman and J. R. Knowles, *J. Am. Chem. Soc.*, 1988, **110**, 1268 and references cited therein.
6 S. P. Harnett and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 1987, 1416; P. M. Cullus, R. Misra and D. J. Wilkins, *J. Chem. Soc., Chem. Commun.*, 1987, 1594; and references cited in these.
7 J. Burgess, N. Blundell, P. M. Cullis, C. D. Hubbard and R. Misra, *J. Am. Chem. Soc.*, 1988, **110**, 7900.
8 A. F. Gerrard and N. K. Hamer, *J. Chem. Soc. B*, 1968, 539; 1969, 369. [In the latter paper the structure of the phosphoramidothioic chloride **4** is erronously shown with a P=O instead of a P=S group.]
9 S. Freeman and M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 2*, 1988, 81.
10 S. Freeman and M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2737.
11 J. A. A. Ketelaar, H. R. Gersmann and K. Koopmans, *Recl. Trav. Chim. Pays-Bas*, 1952, **71**, 1253 (*Chem. Abstr.*, 1953, **47**, 8487); J. R. Cox and O. B. Ramsay, *Chem. Rev.*, 1964, **64**, 317; A. A. Neimysheva, M. V. Ermolaeva and I. L. Knunyants, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1973, **43**, 2589; V. A. Baranskii, G. D. Eliseeva and N. A. Sukhorukova, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1988, **58**, 687; R. D. Cook, S. Farah, L. Ghawi, A. Itani and J. Rahil, *Can. J. Chem.*, 1986, **64**, 1630.
12 W. P. Jencks, *Acc. Chem. Res.*, 1980, **13**, 161; *Chem. Soc. Rev.*, 1981, **10**, 345.
13 S. Freeman and M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1399.
14 A. J. Kirby and A. G. Varvoglis, *J. Am. Chem. Soc.*, 1967, **89**, 415; F. Ramirez, J. F. Marecek and S S. Yemul, *Tetrahedron Lett.*, 1982, **23**, 1515.
15 P. C. Crofts and I. S. Fox, *J. Chem. Soc. B*, 1968, 1416.

Paper 1/01101D
Received 18*th February* 1991
Accepted 8*th March* 1991