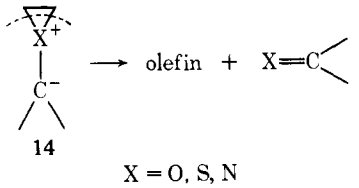


14

X = O, S, N

property exclusive to three-membered ring compounds. The detailed mechanism of the α-fragmentation will be discussed in a full paper in the near future.[9]

Acknowledgment. The authors thank Dr. Y. Onishi of Sagami Chemical Research Center for the supply of 4,4′-dimethoxythiobenzophenone and his valuable discussions.

References and Notes

(1) Paper III: Y. Hata and M. Watanabe, *J. Am. Chem. Soc.*, **95**, 8450 (1973).
(2) Y. Hata and M. Watanabe, *Tetrahedron Lett.*, 3827, 4659 (1972).
(3) A. W. Johnson, "Ylid Chemistry", Academic Press, New York, N.Y., 1966, p 251.
(4) Episulfide was stable to $Cu(acac)_2$ without carbene at reaction condition.
(5) W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, **37**, 1721 (1972), and private communication.
(6) K. Kondo, M. Matsumoto, and A. Negishi, *Tetrahedron Lett.*, 2131 (1972).
(7) The compounds were prepared according to E. E. van Tamelen, *J. Am. Chem. Soc.*, **73**, 3444 (1951); R. Ketchan and V. P. Shah, *J. Org. Chem.*, **28**, 229 (1963).
(8) H. Nozaki, H. Takaya, and R. Noyori, *Tetrahedron*, **22**, 3393 (1966).
(9) σ-HMO calculation[10] for aziridinium ylide was recently accomplished by Dr. M. Yamakawa of Shionogi Research Lab. In the results, it was indicated that the highest occupied orbital of three-membered C–N bonds was clearly antibonding.
(10) T. Yonezawa, H. Yamabe, and H. Kato, *Bull. Chem. Soc. Jpn.*, **42**, 76 (1969).

Yoshiteru Hata,* Masamichi Watanabe
Shionogi Research Laboratory, Shionogi and Company, Ltd. Fukushima-ku, Osaka, 553 Japan

Shodo Inoue
Tokyo Kyoiku University Otsuka, Bunkyo-ku, Tokyo, Japan

Shigeru Oae
The University of Tsukuba 300-31 Ibaraki, Japan

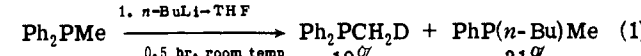
Received January 16, 1975

Nucleophilic Substitution at Phosphorus in Tertiary Phosphines. Inversion of Configuration[1]

Sir:

A number of groups have studied nucleophilic substitution at phosphorus[2] in which the phosphorus atom is tetracoordinated (e.g., phosphonium salts,[3] phosphinate esters,[4] and phosphine oxides[5]), tricoordinated,[6] and pentacoordinated.[7] With few exceptions[3b] the stereochemical course of the substitution has been inversion of configuration at phosphorus.[2a,3c,4] Nucleophilic substitution at phosphorus (S_NP) in tertiary phosphines (carbon leaving group) has been mentioned only in passing.[8]

We have recently reported[9] that treatment of tertiary phosphines with alkyllithium reagents, depending upon the medium employed, can lead to S_NP which is quite competitive with deprotonation (e.g., **1** gives 1.7 times more substitution than deprotonation in THF (eq 1). To our knowledge

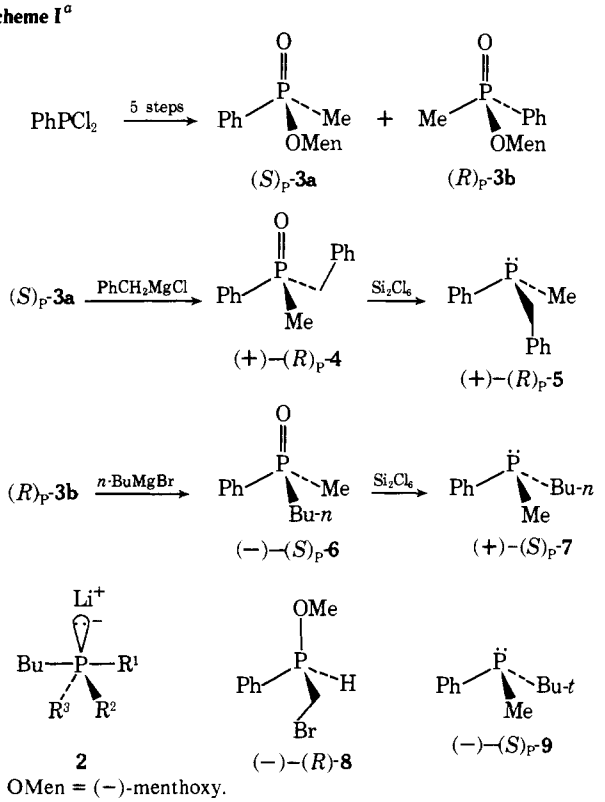


(1)

the only study of the stereochemical course of nucleophilic substitution at tricoordinate phosphorus showed that displacement of chloride ion from 1-chloro-2,2,3,4,4-pentamethylphosphetan by methoxide ion and benzylamine occurs with inversion of configuration at phosphorus.[10] The S_NP process in noncyclic phosphines raised the interesting mechanistic question concerning the nature of the nucleophilic attack on phosphorus. It was conceivable that it could be a direct backside attack (S_NP2, **2** is a transition state), or addition–elimination (**2** is an intermediate), possibly allowing racemization or retention[3b] via pseudorotation, or a frontside attack (known in silicon chemistry[11]). To probe this question we synthesized (+)-$(R)_P$-benzylmethylphenylphosphine (**5**) via the (−)-menthol ester (**3a**)[4a] according to Mislow[12] as outlined in Scheme I. Phosphine **5** ($[\alpha]D^{25}$ +105° (*c* 3.00, $C_6H_5CH_3$), lit.[12] $[\alpha]D$ +81°) was obtained with an enantiomeric excess (ee) ≥95%, as determined by comparison of the NMR spectrum of the phosphonium salt obtained from (+)-**5** and (−)-(*R*)-1-bromo-2-phenyl-2-methoxyethane (**8**),[4b,13] with that obtained from (±)-**5** and **8**.[14] Phosphine (+)-$(S)_P$-**7** ($[\alpha]D^{25}$ + 20.3° (*c* 2.82, C_6H_6)) had 92% ee as determined by the NMR spectra of the phosphonium salts ((+)-**7** + (−)-**8** and (±)-**7** + (−)-**8**).[15] Optically active phosphine **7** has been reported,[16] but no optical rotation data were given. Phosphine (−)-$(S)_P$-**9**[17] was obtained from (+)-$(R)_P$-**5** (vide infra).

Phosphine (+)-$(R)_P$-**5** was subjected to nucleophilic substitution conditions to probe the stereochemistry of the substitution process. Since it was known[9] that the medium can drastically affect the reaction, this was investigated first (Table I). The addition of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) enhances S_NP in less polar solvents for both nucleophiles. The effect is not nearly as pronounced as with **1** as substrate,[9] however, presumably because benzyl anion is a much better leaving group. The

Scheme I[a]



[a] OMen = (−)-menthoxy.

Table I. Yield of Nucleophilic Substitution by Butyllithium at Phosphorus in (+)-$(R)_P$-5 as a Function of Reaction Medium[a]

Medium	*n*-BuLi, yield 7 (%)	*t*-BuLi, yield 9 (%)
THF	39	14
THF–TMEDA	38	16
Et_2O	21	3
Et_2O–TMEDA	50	73
C_6H_{14}	0	2
C_6H_{14}–TMEDA	77	76

[a] The following standard conditions were used: [5] ~0.05 to 0.1 *M*; BuLi introduced as ~1.7 *M* solution in hydrocarbon solvent in nine- to tenfold excess; the reaction was run for 0.50 hr at room temperature, quenched with water, and analyzed by GLPC, using n-$C_{16}H_{34}$ as internal standard; TMEDA:BuLi = 1:1 mole ratio.

TMEDA probably functions as a deag ..ting agent,[18] generating a more nucleophilic anion and a lithium ion more available (than in the aggregates) to participate in the transition state.[9]

When (+)-$(R)_P$-**5** was treated with *n*-BuLi (1.0 g, 4.7 mmol) in THF (conditions as in the footnote of Table I) the lower boiling phosphine **7** was isolated in 18% yield, $[\alpha]D^{25}$ +14.5° (*c* 2.79, C_6H_6), indicating a minimum 66% ee and maximum racemization of 12% (assuming 95% ee in (+)-**5**). The sample contained considerable amounts of low boiling impurities (most of which could be traced back to the BuLi solution), however, as determined by GLPC. A much better indication of optic l purity was obtained from the NMR spectrum of the phosphonium salt of this phosphine and (−)-**8**,[15] which indicated per cent ee at least as great as that of authentic (+)-$(S)_P$-**7** obtained as shown in Scheme I. A similar run using *n*-BuLi in Et_2O–TMEDA with (+)-**5** gave **7** in 28% isolated yield, $[\alpha]D^{25}$ +17.2° (*c* 6.79, C_6H_6) (minimum 78% ee, maximum racemization 8%). Again the NMR spectrum of the phosphonium salt from (−)-**8** indicated ee at least as large as authentic (+)-**7**. Treatment of (+)-$(R)_P$-**5** with *t*-BuLi in Et_2O–TMEDA allowed the isolation of **9** (29%)[17] with a minimum of 71% ee and maximum of 11% racemization. As with **7**, the NMR spectrum of the phosphonium salt from (−)-**8** indicated ≥95% ee.

These data are consistent with S_N^P occurring with complete inversion of configuration at phosphorus, within experimental error. Although the medium and nucleophile have a marked effect on the amount of S_N^P which occurs, these factors apparently do not affect the stereochemical course of the reaction. It is not possible to rule out **2** as an intermediate[19] rather than a transition state; however, it can be concluded that if **2** is an intermediate, the barrier to pseudorotation in this hypervalent anion[7] is high enough that racemization does not occur during its lifetime.

Acknowledgments. I wish to thank Mr. Carl W. Hudson for carrying out some preliminary experiments. Grateful acknowledgement is made to the Robert A. Welch Foundation for support of this research (F-573).

References and Notes

(1) Presented in part at the International Symposium on Nucleophilic Substitution, Pocono Manor, Pa., April, 1975.
(2) The general area of nucleophilic substitution at phosphorus has been studied extensively. For recent reviews, see (a) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus", Elsevier, New York, N.Y., 1967, Chapters 8–10; (b) G. M. Kosolapoff and L. Maier, Ed., "Organic Phosphorus Compounds", Wiley-Interscience, New York, N.Y., Vol. 1–4, 1972; Vol. 5, 6, 1973.
(3) (a) Reference 2a, Chapter 9; (b) R. A. Lewis, K. Naumann, K. E. DeBruin, and K. Mislow, *J. Chem. Soc. D*, 1010 (1969), and references contained therein; (c) P. Beck in ref 2b, Vol. 2, references given on p 212; (d) W. E. McEwen in "Topics in Phosphorus Chemistry", Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N.Y., 1965, p 1.
(4) (a) O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4842 (1968); (b) R. A. Lewis and K. Mislow, *ibid.*, **91**, 7009 (1969).
(5) D. Seyferth, D. E. Welch, and J. K. Heeren, *J. Am. Chem. Soc.*, **86**, 1100 (1964).
(6) (a) K. D. Berlin, T.H. Austin, M. Peterson, and M. Nagabhushanam, *Top. Phosphorus Chem.*, **1**, 17 (1964); (b) ref 2a, Chapter 8.
(7) D. Hellwinkel in ref 2b, Vol. 3, Chapter 5B.
(8) (a) H. Gilman and G. E. Brown, *J. Am. Chem. Soc.*, **67**, 824 (1945); (b) T. V. Talalaeva and K. A. Kocheshkob, *Dokl. Acad. Nauk SSSR*, **77**, 621 (1951); *Chem. Abstr.*, **45**, 10191*i* (1951).
(9) E. P. Kyba and C. W. Hudson, submitted for publication; presented in part at the 30th Southwest Regional Meeting of the American Chemical Society, Dec 1974, Abstract No. 270.
(10) D. J. H. Smith and S. Trippett, *Chem. Commun.*, **855** (1969). We thank the referees for pointing out this work.
(11) L. H. Sommer, "Stereochemistry, Mechanism and Silicon", McGraw-Hill, New York, N.Y., 1965.
(12) K. Naumann, G. Zon, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7012 (1969).
(13) J. P. Casey, R. A. Lewis, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 2789 (1969).
(14) Bromide **8** had $[\alpha]D^{25}$ −74° (c 2.58, MeOH) (lit.[4b,12] $[\alpha]D$ +73° for (*S*)-**8**. In $CDCl_3$, for the phosphonium salt derived from (+)-**5** and (−)-**8**, δ^{MeO} 2.82 ppm, and for (−)-**5** and (−)-**8** (deduced from (±)-**5** and **8**), δ^{MeO} 3.05 ppm.
(15) In $CDCl_3$ for the phosphonium salt derived from (+)-**7** and (−)-**8**, δ^{MeO} 3.06 ppm, and for (−)-**7** and (−)-**8** (deduced from (±)-**7** and **8**), δ^{MeO} 2.95 ppm.
(16) L. Horner and H. Siegel, *Phosphorus*, **1**, 209 (1972).
(17) $[\alpha]D^{25}$ −34° (*c* 3.59, C_6H_6) (lit.[3b] $[\alpha]D$ +29.5° (C_6H_6) (ca. 62% ee) for the $(R)_P$ enantiomer). Because of the small sample size it was difficult to remove all the low boiling impurities by fractional distillation. Another indication of the optical purity of (−)-**9** was obtained from the NMR spectra ($CDCl_3$) of the phosphonium salts from (±)-**9** + (−)-**8** and (−)-**9** + (−)-**8** which indicated >95% ee (δ^{MeO} 2.97 ppm (from (−)-**9**) and δ^{MeO} 2.73 ppm (from (+)-**9** deduced from (±)-**9**)).
(18) A. W. Langer, Ed., *Adv. Chem. Ser.*, **No. 130** (1974).
(19) For evidence for a tetraorganocoordinated phosphorus anion see D. Hellwinkel, *Angew. Chem., Int. Ed. Engl.*, **5**, 968 (1966).

Evan P. Kyba
Department of Chemistry, The University of Texas at Austin
Austin, Texas 78712
Received December 23, 1974

Biosynthesis of *Cephalotaxus* Alkaloids. I. Novel Mode of Tyrosine Incorporation into Cephalotaxine

Sir:

Conifers of the genus *Cephalotaxus* contain a group of unusual alkaloids, the most abundant of which is cephalotaxine (**1**) whose structure and absolute stereochemistry have been determined by X-ray analysis.[1] In *C. harringtonia*, **1** is accompanied by a number of minor alkaloids, including some cephalotaxine derivatives with potent antileukemic activity,[2] and several alkaloids of the homoerythrina type.[3]

The presence of homoerythrina alkaloids such as 3-epischelhammericine (**2**) in *Cephalotaxus* has led to the proposal[3] that both cephalotaxine and the homoerythrina bases may arise from a 1-phenethyl-1,2,3,4-tetrahydroisoquinoline derivative (**3**) via oxidative phenolic coupling. If **3** were

Scheme I