The Stereochemical Course of Migration from Phosphorus to Nitrogen in the Photo-Curtius Rearrangement of Phosphinic Azides (Harger Reaction)

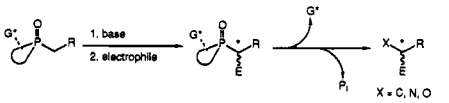
Summary: The homochiral phosphinic azides (*R,R*)-1 and (*S,S*)-1 have been prepared in enantiomerically pure form by resolution of diastereomeric phosphinamides derived from (*S*)-1-phenylethylamine and (*R*)-phenylglycine. Irradiation of the azides in methanol induced a photo-Curtius rearrangement of phosphonamidates in which the stereogenic carbon unit migrated to a nitrogen atom. Hydrolysis of the phosphonamidates produced 1-phenylethylamine, which was 99.0% ee and of the same configuration as the carbon unit in the starting azide (99.0% net retention). The implication for asymmetric synthetic methodology is discussed.

Sir: We are involved in a broadly based program on the development of stereoselective carbon–carbon bond forming reactions using auxiliary-based, chiral, phosphorus-stabilized anions (Scheme I).[1,2] Our interest spans various aspects of this multidimensional problem including: (1) the design of recoverable, chiral auxiliaries, G*, which impart a high degree of diastereoselectivity in carbon–carbon bond formation and which can be readily prepared in optically active form,[1b] (2) spectroscopic and theoretical studies on the structure of phosphorus-stabilized anions,[3] and (3) the development of reactions that allow for the cleavage of the carbon–phosphorus bond with preservation of configuration.[4] In this paper *we report that the transformation of a carbon–phosphorus to a carbon–nitrogen bond in phosphinic derivatives occurs with nearly exclusive retention of configuration.*

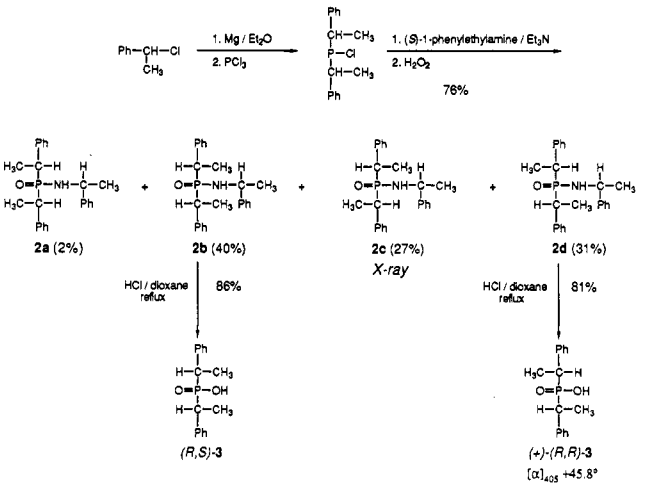
Harger has extensively investigated the chemistry of dialkyl-,[5a-c] diaryl-,[5d] and mixed[5e,5f] phosphinic azides. He found that, while thermally quite stable,[6] these compounds underwent facile photo-Curtius rearrangements. Further, mechanistic studies showed that, as in the photo-Curtius rearrangement of acyl azides,[7] both phosphinoyl nitrenes and excited-state phosphinic azides were primary photoproducts but that rearrangement occurred only in the excited-state azides.[5f] The stereochemical course of migration at the phosphorus center has been studied by Westheimer[8] and Harger,[5b] both of whom demonstrated the intermediacy of metaphosphonimidates, which are trapped by the hydroxylic or amine solvent. The configurational details at the migrating carbon atom have never been established.

Due to the small differences in migratory aptitudes of various groups we chose as our model system the homochiral diastereomer of bis(1-phenylethyl)phosphinic azide, **1**, which has identical flanking groups.[9] The preparation and resolution of **1** is outlined in Scheme II. (1-Phenylethyl)magnesium chloride was treated sequentially with PCl_3, (*S*)-1-phenylethylamine (99.6% ee[10a]), and H_2O_2 to yield (76%) a quaternary mixture of diastereomeric phosphinamides derived from the meso and chiral phosphinic acids. The meso-derived phosphinamides[11] (**2a**, **2b**[12a]) could be separated from the chiral-derived diastereomers (**2c**,[12a] **2d**[12a]) by chromatography. The structure of **2b** was assured by acidic hydrolysis to the meso acid,

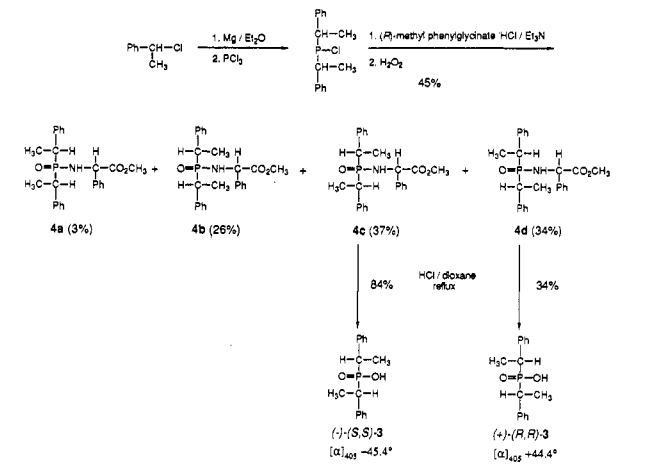
Scheme I



Scheme II



Scheme III



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(3) (a) Cramer, C. J.; Dykstra, C. E.; Denmark, S. E. *Chem. Phys. Lett.* **1987**, *136*, 17. (b) Denmark, S. E.; Cramer, C. J., manuscript submitted.

(4) For a recent disclosure on the stereochemical course of reductive C–P cleavage in bacterial lyase, see: Shames, S. L.; Wackett, L. P.; LaBarge, M. S.; Kuczkowski, R. L.; Walsh, C. T. *Bioorg. Chem.* **1987**, *15*, 366.

(5) (a) Harger, M. J. P. *J. Chem. Soc., Chem. Commun.* **1971**, 442. (b) Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2604. (c) Harger, M. J. P.; Stephen, M. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 736. (d) Harger, M. J. P.; Westlake, S. *Tetrahedron* **1982**, *38*, 1511. (e) Harger, M. J. P.; Westlake, S. *Ibid.* **1982**, *38*, 3073. (f) Harger, M. J. P.; Westlake, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2351.

(6) The remarkable thermal stability of diarylphosphinic azides has been studied: Baldwin, R. A.; Washburn, R. M. *J. Org. Chem.* **1965**, *30*, 3860.

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(8) Wiseman, J.; Westheimer, F. H. *J. Am. Chem. Soc.* **1974**, *96*, 4262.

(9) This set of phosphinic acid derivatives has the same intriguing symmetry properties as the 1,2,3-trihydroxyglutaric acids discussed by Mislow. Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

(10) Enantiomeric excess determined by the method of Pirkle: Pirkle, W. H.; Mahler, G.; Hyun, M. H. *J. Liquid Chromatog.* **1986**, *9*, 443. (a) L-Naphthylalanine column. (b) D-Naphthylalanine column.

(11) The configurations of the stereogenic carbon centers in **2a**, **2b**, **4a**, and **4b** have not been established.

(12) (a) This compound was fully characterized by ^1H and ^{13}C NMR, IR, MS, elemental analysis (±0.4%), and optical rotation. (b) Full characterization on the racemic and (except for MS) optically active material. (c) Full characterization of the racemic material. (d) ^1H NMR, IR, and rotations were obtained for optically active samples.

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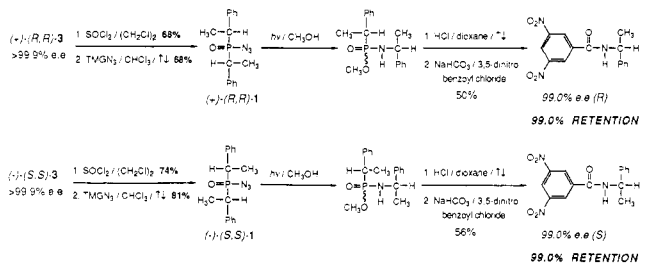
Scheme IV



(R,S)-**3**[12a] (mp 157–158 °C), which has been synthesized by an independent route.[13] Unfortunately, the resolution of the desired diastereomers required extensive and sacrificial purification, which afforded only **2d** in sufficient quantities for further studies. However, a sample of **2c** provided a crystal suitable for X-ray structure analysis,[14] which allowed assignment of the absolute configurations of **2c** and **2d** as S,S and R,R, respectively. Acidic hydrolysis of **2d** afforded a dextrorotatory acid (+)-(R,R)-**3**[12b] ($[\alpha]^{30}_{405}$ +45.8°, mp 192 °C), which was shown to be of >99.9% ee by HPLC analysis[10b] of a derived 2,4-dinitroanilide.[12c]

The enantiomeric acid could be obtained in larger quantities by a similar resolution sequence using (R)-methylphenylglycinate (>99.9% ee[10a]) as shown in Scheme III.[15] In this case the desired diastereomer, **4c**,[12a] could be separated from **4d**,[12a] but it was always contaminated with traces of **4a** (1.2%). Acidic hydrolysis of **4c** provided a levorotatory acid (−)-(S,S)-**3**[12c,d] ($[\alpha]^{29}_{405}$ −45.4°, mp 192–192.5 °C). The meso contaminants were easily removed at the azide stage.

The phosphinic azides (R,R)-**1**[12b] and (S,S)-**1**[12c,d] were prepared by conversion of the acids to the (R,R)-[12b] and (S,S)-phosphinic chlorides[12c,d] followed by treatment with tetramethylguanidinium azide ($TMGN_3$) (Scheme IV). The chiral azides were assumed to have the same ee as the starting acids since no epimerization was detected as indicated by the absence of meso azides.

The phosphinoyl photo-Curtius rearrangements were performed by irradiation of the azides in methanolic solution at 254 nm. The concentrated photolysate containing a mixture of the P-epimeric phosphonamidates was hydrolyzed with acid, and the 1-phenylethylamine released was isolated by derivatization as the 3,5-dinitrobenzamide under Shotten–Baumann conditions (overall yield 50–56%).[16] HPLC analysis of the 3,5-dinitrobenzamide from the rearrangement of (R,R)-**1** showed a 99.0% ee of (R)-1-phenylethylamine while the product of rearrangement of (S,S)-**1** showed an identical 99.0% ee of the (S)-antipode. Since both starting azides were enantiomerically pure, this corresponds to migration of the carbon center with *99.0% net retention of configuration.* These results accord well with the classic studies by Kenyon[17] on the stereochemical course of migration in the thermal Curtius rearrangement of acyl azides, which also occurs with nearly complete retention of configuration. The photo-Curtius rearrangement of acyl azides has not been explicitly stereochemically defined, but retention of configuration has been documented in isolated cases.[18]

The demonstrated ability to selectively excise the phosphorus unit provides great impetus for the development of chiral prosthetic groups, which will control the creation of C–C single bonds next to the phosphorus. This also serves to illustrate one of the important advantages of phosphorus compared to sulfur-based methods. We are extending these studies to establish the stereochemical detail in the base-induced Lossen rearrangement of phosphinoyl hydroxylamines[19] and dyotropic rearrangement of phosphinic peroxides.[20] In addition, we will be investigating the corresponding reactions in a *phosphonic* model system.

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Supplementary Material Available: Full characterization data for (+)-**1**, (−)-**1**, **2a–d**, (+)-**3**, (−)-**3**, and **4b–d** is provided along with a procedure for the phosphinoyl photo-Curtius rearrangements of (+)-**1** and (−)-**1** (12 pages). Ordering information is given on any current masthead page.

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(13) Dorow, R. L., unpublished results from these laboratories.
(14) Refinement of the crystallographic analysis was extremely difficult due to the presence of four molecules in each unit cell (space group P_1) in different conformations.
(15) Due to chromatographic coincidences it was not possible to obtain both antipodes from a single resolution method.
(16) Control experiments showed that no isomerization occurred after the rearrangement.
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(18) (a) ApSimon, J. W.; Edwards, O. E. *Can. J. Chem.* **1962**, *40*, 896. (b) Meyer, W. L.; Levinson, A. S. *J. Org. Chem.* **1963**, *28*, 2859. (c) Brown, R. F. C. *Aust. J. Chem.* **1964**, *17*, 47.
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Anthrones as Reactive Dienes in Diels–Alder Reactions

Summary: Anthrone and related phenols and hydroquinones exhibit solvent-dependent high diene reactivity in Diels–Alder reactions; evidence for a catalytic oxyanion accelerated pathway is presented.

Sir: In order to be of maximum value as an olefin protecting group, a 1,3-diene must: (1) exhibit high Diels–Alder reactivity; (2) form cycloadducts that are not readily degraded by functional-group interconversions; and (3) give cycloadducts that undergo facile retro-Diels–Alder reactions under specific conditions. Anthracenes meet the second requirement well, as first illustrated by Diels and Thiele in 1938.[1] Recently Knapp et al.[2] demonstrated very

(1) Diels, O.; Thiele, W. E. *Chem. Ber.* **1938**, *71*, 1173; we wish to thank a referee for pointing out this early example. The use of arenes in cycloaddition reactions is the subject of a review: Wagner-Jauregg, T. *Synthesis* **1980**, 165.

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