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A Novel Resolution Procedure for the Preparation of P-Stereogenic Phosphine Oxides

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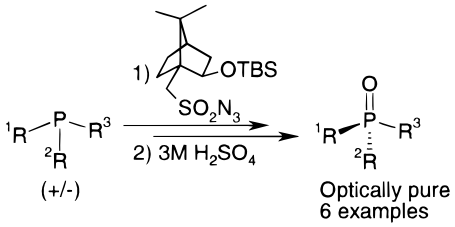
ABSTRACT



A new general route for preparing enantiomerically pure P-stereogenic phosphine oxides has been developed by exploiting the Staudinger reaction between racemic tertiary phosphines and an enantiomerically pure organoazide. The resulting phosphinimines are easily resolved by either crystallization or flash chromatography and serve as synthetic intermediates toward enantiomerically pure phosphine oxides.

Asymmetric synthesis mediated by transition metals bearing enantiomerically pure phosphine ligands has become a cornerstone of organic chemistry and has allowed for the preparation of a variety of complex natural products.[1] As a result, much effort has been directed toward the rational design, synthesis, and testing of new enantiomerically pure phosphines for various synthetic purposes. A diverse range of enantiomerically pure phosphines is now commercially available, and numerous other ligands have been reported in the literature.[2] Among these known phosphines, however, the vast majority of examples are predicated upon carbon-based central or axial chirality rather than asymmetry about a tetrahedral phosphorus atom. The low abundance of P-stereogenic phosphines for asymmetric transformations is due, in part, to the relative difficulty of obtaining such compounds by resolution procedures or diastereoselective synthesis.[3] While there have been several recent advances in the diastereoselective synthesis of P-stereogenic materials,[4] there are still relatively few resolution methods available for obtaining enantiomerically pure tertiary phosphines. We herein report a new, simple, and effective method for obtaining P-stereogenic phosphine oxides using an enantiomerically pure organoazide resolving agent.

We rationalized that a Staudinger reaction between a racemic tertiary phosphine and an enantiomerically pure azide could potentially furnish a 1:1 mixture of diastereomeric phosphinimines if the P═N bond rotational barrier was low enough to prevent geometrical isomerism.[5] To our delight, treatment of racemic phosphine **1a** with (1*S*)-camphorsulfonyl azide **2**[6] afforded an equimolar mixture of dia-

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(1) Stephenson, G. R. *Advanced Asymmetric Synthesis*; Chapman & Hall: New York, 1996 and references therein.

(2) For reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, 1994; Chapter 2. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: Weinheim, 1993; Chapter 1. (c) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1985; Vol. 5, Chapter 1.

(3) Pietrusiewicz, K. M.; Zablocka M. *Chem. Rev.* **1994**, *94*, 1375.

(4) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279.

(5) The calculated P═N rotational barrier is ca. 2.54 kcal/mol. See: Koketsu, J.; Ninomiya, Y.; Suzuki, Y.; Koga, N. *Inorg. Chem.* **1997**, *36*, 694 and references therein.

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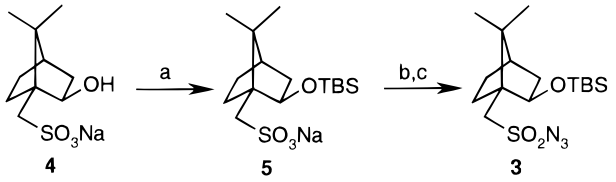
stereomeric phosphinimines, without complication by potential bond isomers, as evidenced by ^{1}H and ^{31}P NMR analysis. However, conditions could not be found to separate the resulting mixture by chromatography or crystallization. This disappointing result led us to screen a variety of other enantiomerically pure azides[7] in hopes of finding an efficient resolving agent. We were pleased to find that the diastereomeric phosphinimines produced from the reaction of (1*S*,2*R*)-*O*-(*tert*-butyldimethylsilyl)isobornyl-10-sulfonyl azide (**3**) with various racemic phosphines were easily separable by fractional crystallization or flash chromatography.

This new, effective resolving agent can easily be prepared on a large scale by the three-step sequence shown in Scheme 1 from known isoborneol derivative **4**.[8]

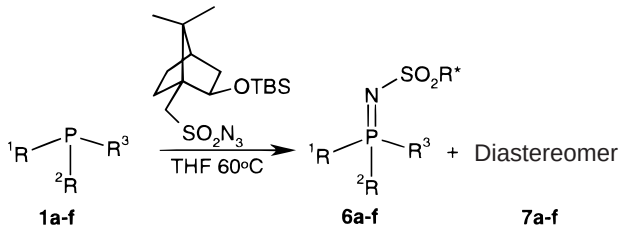
Scheme 1. Synthesis of the Resolving Agent[9 a]



[a] Reagents and conditions: (a) TBSCl, Et_3N, DMF, rt, 3 h; (b) $SOCl_2$, C_6H_6, DMF; reflux 12 h; (c) NaN_3, DMA, H_2O, 60 °C 12 h, 57% isolated yield from **4**.

Treatment of racemic phosphines[10] **1a**−**f** with (1*S*,2*R*)-sulfonyl azide **3** in THF at 60 °C smoothly affords the desired phosphinimine mixtures[11] in high yield (Table 1). Separation

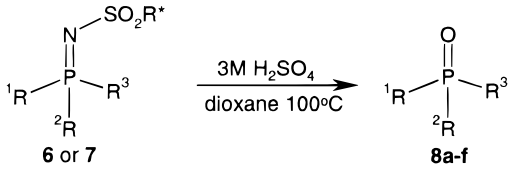
Table 1. Treatment of Racemic Phosphines with Azide **3**[14]



entry	R^1	R^2	R^3	yield (%)
1a	Ph	Me	C_6H_{11}	94
1b	Ph	Me	C_5H_9	90
1c	Ph	Me	$CH(CH_3)_2$	87
1d	Ph	Me	1-naphthyl	94
1e	Ph	Me	9-phenanthryl	89
1f	Ph	1-naphthyl	*p*-PhC_6H_4	91

of the resulting mixtures may be accomplished by fractional crystallization from petroleum ether or acetonitrile.[12] In some cases, resolution may be obtained by simple flash chromatography using hexane/ethyl acetate eluent mixtures.[13] Only in the case of isopropylmethylphenylphosphine (**1c**) could the diastereomers not be fully separated since the first diastereomer to crystallize was always found to contaminate the mother liquor to a small degree.[15] Cleavage of the isomerically pure phosphinimines via acid hydrolysis was found to afford stereochemically pure[16] phosphine oxides **8a**−**f** (Table 2), which were easily separated from the sulfonamide byproduct[17] via column chromatography.

Table 2. Hydrolysis of Isomerically Pure Phosphinimines



SM	R^1	R^2	R^3	yield (%)
6a	Ph	Me	C_6H_{11}	93
7b	Ph	Me	C_5H_9	93
6c	Ph	Me	$CH(CH_3)_2$	94
6d	Ph	Me	1-naphthyl	96
6e	Ph	Me	9-phenanthryl	>99
7f	Ph	1-naphthyl	*p*-PhC_6H_4	93

To investigate the stereochemical course of the hydrolysis step, a single-crystal X-ray structure determination of phosphinimine **6c** was performed from which the absolute configuration of the phosphorus center was determined to have *R* configuration (Figure 1).

(6) Cremlyn, R.; Burrell, K.; Fish, K.; Hough, I.; Mason, D. *Phosphorus Sulfur* **1982**, *12*, 197.

(7) Alkyl azides such as (+)-neomenthyl azide, 3α-azido-5α-cholestane, and 6-azido-6-deoxy-1,2,3,4-di-*O*-isopropyliden-α-D-galactopyranose were found to be unsuitable resolving agents since the resulting phosphinimine mixtures were generally less stable toward storage or flash chromatography.

(8) Dimmel, D. R.; Fu, W. Y., *J. Org. Chem.* **1973**, *38*, 3782.

(9) **Selected spectral data for azide 3:** $\alpha^{20}_D = -36.2°$ ($c = 5.5$, $CHCl_3$); IR (KBr) cm^{-1} 2131; ^{1}H NMR (200 MHz) δ 4.06 (m, 1H), 3.97 (d, J = 14.0, 1H), 3.12 (d, J = 14.0 Hz, 1H), 2.10−1.88 (m, 1H), 1.86−1.49 (m, 4H), 1.47−1.06 (m, 3H), 1.05 (s, 3H), 0.90 (s, 9H), 0.89 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (50 MHz) δ 75.8, 54.9, 50.4, 49.3, 44.5, 41.9, 28.6, 27.2, 25.8, 20.6, 20.1, 17.8, −4.1, −5.4; exact mass calcd for $C_{16}H_{31}N_3O_3SSi - C_4H_9$ 316.1151, found 316.1120.

(10) Racemic phosphines were prepared via known general methods, see: (a) Payne, N. C.; Stephan, D. W. *Can. J. Chem.* **1980**, *58*, 15. (b) Bestman, H. J.; Lienert, J.; Heid, E. *Chem. Ber.* **1982**, *115*, 3875. (c) Wittig, G.; Braun, H.; Cristau, H. *Liebigs Ann. Chem.* **1971**, *751*, 17.

(11) Analytical samples of all new compounds were obtained by crystallization or flash chromatography. The structure assigned to each compound was in accord with its spectral (^{1}H, ^{13}C, and ^{31}P NMR, IR, and MS) characteristics including suitable combustion analysis (C, H) and/or high-resolution mass spectral analysis.

(12) Entries **1a**−**1c** of Table 1 were separated by fractional crystallization.

(13) Entries **1d-1f** of Table 1 were separated by flash chromatography.

(14) **Typical Procedure.** Azide **3** (0.410 g, 1.10 mmol) in THF (2.5 mL) was added dropwise to the starting phosphine (1.00 mmol) in THF (2.5 mL). The resulting mixture was then heated (60 °C, 12 h) and subsequently concentrated in vacuo. The crude phosphinimines thus obtained were separated by crystallization or flash chromatography. The yield reported in Table 1 is the combined isolated yield of **6** and **7**. In each case, compound **6** was assigned as the first isomer to crystallize or elute from the column.

(15) The phosphinimine purity is easily determined by ^{1}H and ^{31}P NMR analysis. Compound **7c** was obtained as a ca. 7:1 mixture with isomer **6c**.

(16) Optical rotation data for the phosphine oxides closely matched the reported values. See Table 3.

(17) At present, we have not found a suitable method for recycling the resolving agent.

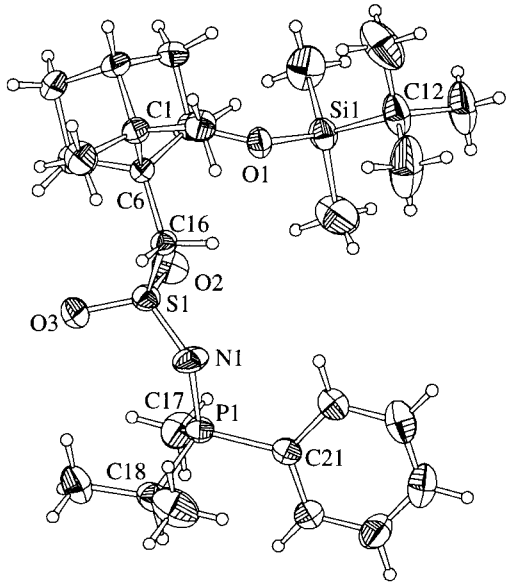


Figure 1. ORTEP drawing of phosphinimine **6c**[18] drawn with 30% probability ellipsoids, except for the hydrogen atoms which are represented as spheres of arbitrary size.

Treatment of phosphinimine **6c** with 3 M H_2SO_4 in refluxing 1,4-dioxane for 12 h furnished (−)-phosphine oxide **8c** known to be of *S* configuration.[19] Hence the phosphinimine hydrolysis proceeds stereospecifically with inversion of configuration. Moreover, this relationship, in conjunction with literature data, may be used to unambiguously assign some of the phosphinimine absolute configurations (Table 3). Although the stereochemical configuration and optical rotation data have not been reported for phosphine oxides **8b** and **8e**, we are confident that we have obtained these compounds in optically pure form on the basis of the good agreement observed in the optical rotation data for known oxides **8a**, **8c**−**d**, and **8f**. In addition, we found that the phosphine oxide obtained from the hydrolysis of **6b** or **6e** exhibited a rotation equal in magnitude but opposite in sign to the hydrolysis product of **7b** or **7e**, respectively.

Table 3. Assignment of Phosphinimine Absolute Configuration from Hydrolysis Product Optical Rotation Data

			configuration	
SM	yield (%)	product α^{20}_D (*c*, solvent)	product **8**	SM
6a	93	+19.2 (0.93, MeOH)[21]	R_P	S_P
7b	93	+33.3 (1.62, MeOH)		
6c	94	−22.6 (1.00, MeOH)[22]	S_P	R_P
6d	96	+19.8 (2.92, MeOH)[23]	S_P	R_P
6e	>99	+71.4 (1.14, MeOH)[24]		
7f	93	+26.9 (0.62,$CHCl_3$)[25]	R_P	S_P

Since reliable methods have been developed to stereospecifically reduce phosphine oxides to the corresponding phosphines with either retention or inversion of configuration at phosphorus,[20] our new resolution protocol also serves as a route to enantiomerically pure tertiary phosphines. We are currently investigating the direct reduction of phosphinimines **6a**−**f** and **7a**−**f** to give enantiomerically pure phosphines. The results of these studies will be disclosed elsewhere.

In summary, we have developed a novel, facile method for the resolution of P-stereogenic phosphine oxides using a Staudinger reaction with enantiomerically pure organoazide **3**. The resulting phosphinimine diastereomers may be separated by crystallization or flash chromatography and used as synthetic intermediates toward enantiomerically pure phosphine oxides and phosphines.

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Supporting Information Available: Experimental procedure for the preparation of **3**, characterization data for compounds **3**, **6a**−**f**, **7a**−**b**, **7d**−**f**, and **8b**, and X-ray data for compound **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Compound **6c**: orthorhombic $P2_12_12_1$ (No. 19); a = 12.337(4) Å, b = 12.833(3) Å, c = 18.751(2) Å; V = 2969(1) Å^3; Z = 4; R = 0.0459; wR = 0.1208; Flack parameter [Flack, H. D. *Acta Crystallogr*. **1983**, *A39*, 876] = −0.03(2). Bijvoet analysis was performed. A refinement of the inverted structure was carried out and converged with R = 0.0543, wR = 0.1427 with Flack parameter = 1.03(3) and was therefore rejected as the absolute configuration present in the crystal.

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(20) See: (a) Horner, L.; Balzer W.-D., *Tetrahedron Lett.* **1965**, 1157. (b) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012. (c) Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265. (d) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 2788.

(21) α^{20}_D +19.0° in MeOH; (+)-*R*. Korpium, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842.

(22) α^{20}_D −21.2° in MeOH; (+)-*R*. Byrne, L. T.; Engelhardt, L. M.; Jacobsen, G. E.; Leung, W.-P.; Papasergio, R. I.; Raston, C. L.; Skelton, B. W.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1989**, 105.

(23) α^{20}_D −19.8° in MeOH; (+)-*S*. Luckenbach, R. *Phosphorus* **1972**, *5*, 223.

(24) Although methyl-9-phenanthrylphenylphosphine oxide has appeared numerous times in the literature, to our knowledge no optical rotation data has been reported for this compound.

(25) α^{32}_D −27.0° in MeOH. Tani, K.; Brown, L. D.; Ahmed, J.; Ibers, J. A.; Yokota. M.; Nakamura, A.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 7876.