P[(*S*,*S*,*S*)-PhHMeCNCH$_2$CH$_2$]$_3$N: A New Chiral ^{31}P and ^{1}H NMR Spectroscopic Reagent for the Direct Determination of *ee* Values of Chiral Azides

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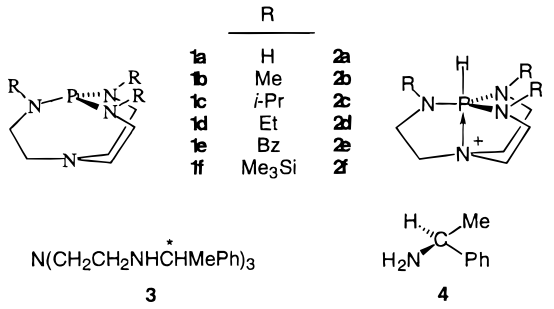
A facile and economical procedure for the synthesis of the C_3 chiral α-phenylethylamino trisaminoamine [(*S*,*S*,*S*)-PhHMeCNHCH$_2$CH$_2$]$_3$N in good yield is reported. The corresponding bicyclic proazaphosphatrane P[(*S*,*S*,*S*)-PhHMeCNCH$_2$CH$_2$]$_3$N, its bicyclic phosphoryl derivative, and its tricyclic P-protonated azaphosphatrane were also synthesized and characterized. It is found that the proazaphosphatrane is an efficient derivatizing agent for the direct determination of enantiomeric ratios of chiral azides by means of ^{31}P and ^{1}H NMR spectroscopy.

Introduction

In recent years we have been exploring the chemistry of proazaphosphatranes such as **1a**−**f**,[1−6] some of which are proving to be exceedingly potent catalysts, promoters and strong nonionic bases that facilitate a variety of useful organic transformations. For example, **1b** is an



efficient catalyst for the trimerization of aryl and alkyl isocyanates that function as additives in the manufacture of nylon-6,[7] for the protective silylation of a wide variety of sterically hindered and deactivated alcohols,[8] and for the acylation of such substrates.[9] Proazaphosphatrane **1b** is much stronger as a base than DBU,[10] a commonly used nonionic base in organic synthesis. Thus it is a superior base for the synthesis of porphyrins,[11] for the dehydrohalogenation of secondary and tertiary halides,[12] and for the synthesis of a chiral fluorescence agent.[13] As a result of such applications, **1b** has become commercially available.[14] Recently, we have discovered that **1b** and **1c** are also efficient nonionic base catalysts for transesterification,[15] *β*-nitroalkanol synthesis,[16] Michael additions,[17] *β*-hydroxy nitrile synthesis,[18] and α,*β*-unsaturated nitrile synthesis.[19]

Chiral azides are important starting materials for the synthesis of amines that are used as ligands, chiral auxiliaries, pharmaceutical intermediates and building blocks for the asymmetric synthesis of natural products.[20] Although amines can be made in several ways, the azide reduction method is often employed because it is facile and well documented in the literature. Hence numerous methods have been developed to synthesize azides in enantiomeric forms.[21] While a variety of approaches can be taken to establish the enantiomeric purity of chiral compounds, ^{31}P NMR spectroscopic analysis is very popular because of the attractive features of this nucleus.[22] Several derivatizing agents have been developed for such analyses of chiral alcohols, amines, and thiols.[21e] However, no derivatizing agent has been reported for the

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(1) Verkade, J. G. *Acc. Chem. Res.* **1993**, *26*, 483.
(2) Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233.
(3) Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163.
(4) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.
(5) Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69.
(6) Liu, X.; Bai, Y.; Verkade, J. G. *J. Organomet. Chem.* **1999**, *582*, 16.
(7) Tang, J.-S.; Mohan, T.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931.
(8) D'Sa, B.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 832.
(9) D'Sa, Bosco A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.
(10) Tang, J.-S.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.
(11) Tang, J.-S.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793.
(12) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. *Heteroat. Chem.* **1996**, *7*, 455.
(13) Tang, J.-S.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 8750.
(14) Strem Chemical Company. 7 Mulliken Way, Dexter Industrial Park, Newburyport, MA 01950·4098.
(15) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.
(16) Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298.
(17) Kisanga, P.; Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.*, submitted for publication.
(18) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.
(19) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.
(20) (a) Jadhav, P. K.; Man, H, W. *Tetrahedron Lett.* **1996**, *37*, 1153. (b) Lundquist, J. T.; Dix, T. A. *Tetrahedron Lett.* **1998**, *39*, 775. (c) Corey, E. J.; Link, O. *J. Am. Chem. Soc.* **1992**, *114*, 1906. (d) Skarzewski, J.; Gupta, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1861. (e) Brunner, H.; Bugler, H.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699. (f) Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023.
(21) (a) Mitrochkine, A. A.; Blain, I.; Bit, C.; Canlet, C.; Pierre, S.; Courtieu, L.; Reglier, M. *J. Org. Chem.* **1997**, *62*, 6204. (b) Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1699. (c) Trost, B. M.; Pulley, S. R. *Tetrahedron Lett.* **1995**, *36*, 8737. (d) Besse, P.; Veschambre, H.; Chenevert, R.; Dickman, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1727. (e) Mischitz, M.; Faber, K. *Tetrahedron Lett.* **1994**, *35*, 81. (f) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213. (g) Sato, T.; Mizutani, T.; Okumura, Y.; Fujisawa, T. *Tetrahedron Lett.* **1989**, *30*, 3701. (h) Fadnavis, N. M.; Vadivel, S. K.; Sharfuddin, M.; Bhalerao, U. T. *Tetrahedron: Asymmetry* **1997**, *8*, 4003. (i) Besse, P.; Veschambre, H.; Dickman, M.; Chenevert, R. *J. Org. Chem.* **1994**, *59*, 8288.

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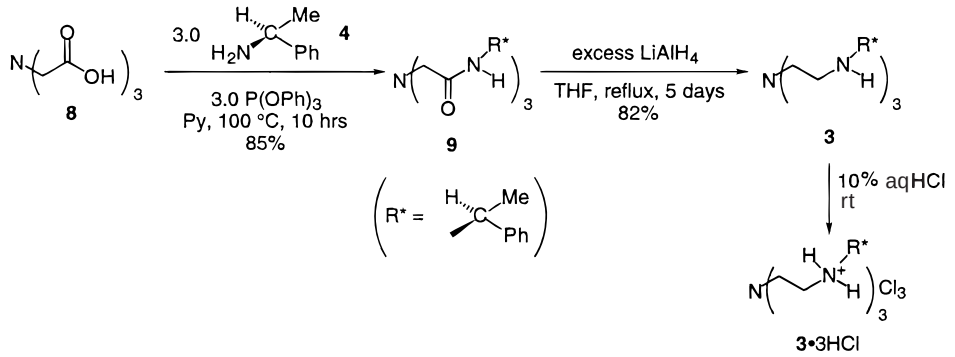
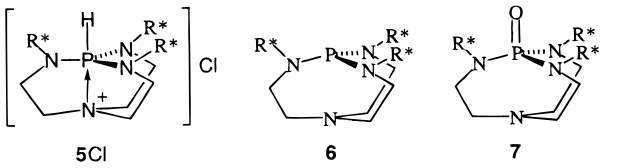
Scheme 1



direct determination of *ee* values of chiral azides by means of ^{31}P or ^{1}H NMR spectroscopy.

We report herein a simple and efficient procedure for the synthesis of the C_3 chiral tripodal trisaminoamine **3** from commercially available inexpensive (*S*)-α-phenylethylamine **4**, and the conversion of **3** to the corresponding tricyclic azaphosphatrane **5**(Cl), which can be deprotonated to the bicyclic proazaphosphatrane **6**. The new chiral nonionic base **6** is found to be an excellent tagging agent for the direct determination of enantiomeric excesses of chiral azides using ^{31}P and ^{1}H NMR spectroscopy. Upon oxidation, proazaphosphatrane **6** yields the new C_3 chiral phosphine oxide **7**.

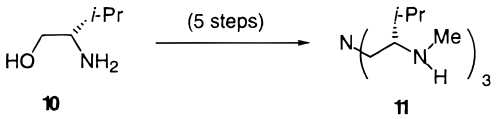


Results and Discussion

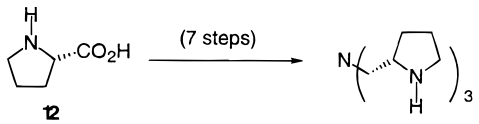
Synthesis of 3. The synthetic route to the chiral trisaminoamine **3** is shown in Scheme 1. In the first step, nitrilotriacetic acid **8** is condensed with 3.0 equiv of **4** in the presence of $P(OPh)_3$ using pyridine as the solvent at 100 °C to give (*S*,*S*,*S*)-amidoamine **9**. The synthesis of **9** reported earlier[23] required tedious column chromatography for purification, and the yield was only moderate (65%). In the present work, spectroscopically pure **9** was obtained in good yield (85%) upon recrystallization from THF/hexanes at −20 °C. To ensure complete reduction of all three amido groups of **9** to give optically pure **3**, it was necessary to carry out the second step in the presence of excess $LiAlH_4$ in refluxing THF for 5 days. The yield of **3** (82%) is surprisingly good.

The only two tripodal chiral trisaminoamines that have been reported possess chiral centers at the β carbon of the tertiary nitrogen[24,25] as shown in Schemes 2 and 3.

Scheme 2



Scheme 3



The synthesis of **11** involves nucleophilic ring opening of the aziridine derived from **10**.[24] The drawbacks of this synthesis are that the enantiopure amino alcohol used as the starting material is expensive, and five steps are required to obtain the desired product. Although (*S*)-proline **12**, the starting material for **13**, is readily available and inexpensive, seven synthetic steps are required to obtain the final product, including two condensations, three $LiAlH_4$ reductions, a protection, and a deprotection.[25] By contrast, our route to **3** utilizes inexpensive nitrilotriacetic acid **8** and (*S*)-(−)-α-phenylethylamine **4**, only two steps are required to obtain the final product, and the workup is quite simple, involving only extraction and recrystallization. Moreover, the chiral substituents can be readily replaced with other chiral amines to tune the steric and electronic properties of the proazaphosphatrane derivatives. Chiral **3** represents the first example of a tripodal trisaminoamine in which the chiral centers are not on the CH_2CH_2 moiety.

Synthesis of 5(Cl), 6, and 7. The protonated azaphosphatrane **5**(Cl) shown in Scheme 4 was synthesized according to our established procedure for analogues of this cation.[3] However, formation of the tricyclic phosphatrane cage was not complete even after 1 week of reaction. Thus only 75% conversion and a 62% isolated yield were realized, which is considerably lower than the 95% conversion and 90% isolated yield for the analogous synthesis of **2b**. Raising the temperature to 60 °C gave no improvement in either yield or purity of the product. The main impurity is **3**·3HCl (see Experimental Section). The formation of **3**·3HCl may be due to steric hindrance of the α-phenylethyl groups, which could lower the rate of cage formation relative to protonation of **3**. In the presence of KO-*t*-Bu, using THF as the solvent, **5**(Cl) was easily converted into proazaphosphatrane **6** in 82% yield within 2 h. Oxidation of **6** with $(Me_3SiO)_2$ in benzene gave **7** in 90% yield.

Structural Considerations. The computer drawing

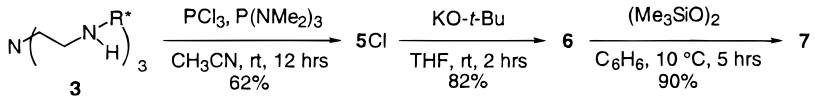
(22) (a) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J.-F.; Lellouche, J.-P. *J. Org. Chem.* **1989**, *54*, 2420. (b) Mangeney, P.; Alexakis, A. *Tetrahedron: Asymmetry* **1993**, *4*, 2431. (c) Mangeney, P.; Mutti, S.; P.; Alexakis, A. *J. Org. Chem.* **1992**, *57*, 1224. (d) Alexakis, A.; Mutti, S.; P.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326. (e) Hulst, R.; Koen de Vries, N.; Feringa, B. L *Tetrahedron: Asymmetry* **1994**, *5*, 669. (f) Devitt, P. G.; Mitchel, M. C.; Weetman, J. M.; Tayler, R. J.; Kee, T. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.

(23) Hammes, B. S.; Ramos-Maldonado, D.; Yap, G. P. A.; Liable-Sands, L.; Rheingold, A. L.; Young, V. G.; Borovik, A. S. *Inorg. Chem.* **1997**, *36*, 3210.

(24) Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1998**, *8*, 2655.

(25) Ishihara, K.; Karumi, Y.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 5692.

Scheme 4



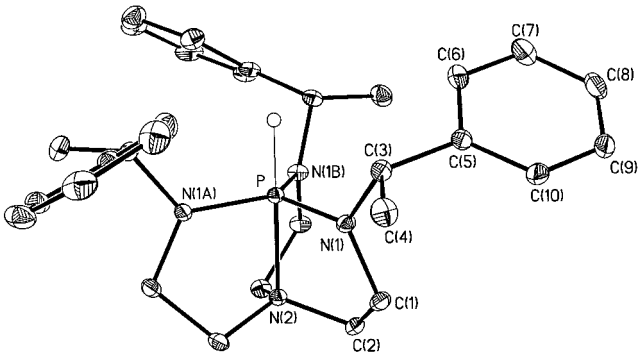


Figure 1. The molecular structure of cation **5** of **5**(Cl) drawn with the thermal ellipsoids at the 30% probability level. All hydrogen atoms except the H atom on the phosphorus were omitted for clarity.

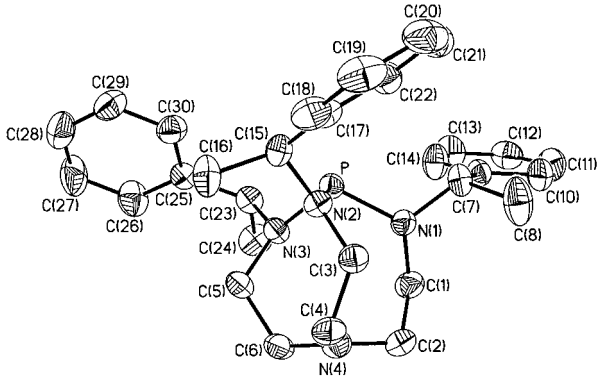


Figure 2. The molecular structure of **6** drawn with the thermal ellipsoids at the 30% probability level. The hydrogen atoms have been omitted for clarity.

of **5**(Cl) in Figure 1 features a P−N_{ax} distance of 1.967(10) Å (which is 40% shorter than the sum of the P and N van der Waals radii[26]), a nearly tetrahedral bridgehead nitrogen [av ∠$CN_{ax}C$ = 112.54(7)°], and a nearly ideal trigonal bipyramidal phosphorus with N_{eq}−P−N_{eq} angles averaging 119.4(10)°. All these metrics are consistent with a fully transannulated structure. The P−N_{ax} distance of cation **5** is within experimental error of those of the less sterically hindered analogues **2b**[26] and **2c**[5] (as judged by the 3 × esd criterion). The remaining bond distances and angles (Table 2) are unremarkable, and the crystallographic data are collected in Table 3.

Compound **6** is the first example of a chiral proazaphosphatrane characterized by X-ray crystallography (Figure 2). Its geometry around P is pyramidal [av ∠N_{eq}-PN_{eq} = 104.16(14)°], but the bridgehead axial nitrogen (angle sum = 357.3°) possesses an essentially planar configuration. This planarity is attributed to van der Waals repulsions among the methylene protons adjacent to the bridgehead nitrogen, which tend to draw the nitrogen from a downward directed pyramidal sp^3 geometry into a hybridized nearly planar sp^2 geometry.[5] The

(26) Lensink, C.; Xi, S. K.; Verkade J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478.

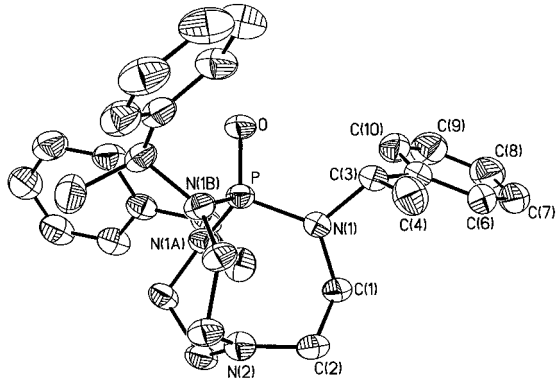
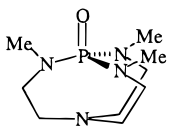


Figure 3. The molecular structure of **7** drawn with the thermal ellipsoids at the 30% probability level. The hydrogen atoms have been omitted for clarity.

transannular N−P distance of 3.274 Å in **6** is only about 2% shorter than the van der Waals sum of 3.35 Å and is very close to that of **1c**[5] (3.293 Å). The remaining bond distances and angles are unremarkable (Table 4), and the crystallographic data are collected in Table 3.

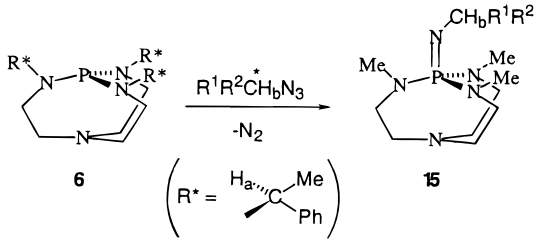
Like its nonchiral analogue **14**,[7] compound **7** (Figure 3) displays a nearly tetrahedral geometry around the bridgehead P [av ∠$N_{eq}PN_{eq}$ = 107.81(13)°] and a nearly planar trigonal geometry around the bridgehead nitrogen [av ∠$CN_{ax}C$ = 119.999(6)°], compared with 107.6(1)° and 118.9(2)°, respectively, in **14**.[7] The P−N_{ax} distance in **7**



14

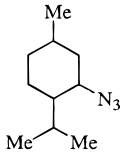
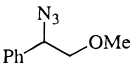
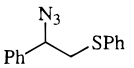
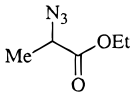
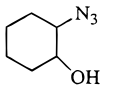
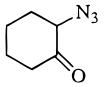
[3.081(5) Å] is about 8% shorter than the sum of the P and N van der Waals radii, but it is still very close to the P−N_{ax} distance in **14** [3.152(3) Å].[7] The remaining bond distances and angles (Table 5) are unremarkable, and crystallographic data are summarized in Table 3.

Proazaphosphatrane 6 as a Chiral Derivatizing Agent for Chiral Azides. In previous work[10] we showed that proazaphosphatrane **1b** reacts with organic azides to give iminophosphines quantitatively. In the present work, diastereomeric iminophosphine derivatives were quantitatively prepared by heating the chiral proazaphosphatrane **6** with enantiomeric mixtures of azides in C_6D_6 at 50 °C in an NMR tube for 2 h, as represented in reaction 1. The ^1H and proton-decoupled ^{31}P NMR spectra



(1)

Table 1. ^{31}P and ^{1}H NMR Data for Azides Derivatized by 6

substrate		actual ratio	$\delta^{31}P$ ($\Delta\delta$) (ppm)[a]	$\delta^{1}H$ ($\Delta\delta$) (ppm)[b]	measured ratio[c]
	**17**[d]	racemic	31.98 (1.14)	4.21 (0.14)	49.0:51.0 (49.1:50.9)
		(-)isomer[e]	32.66	4.18	100 : 0
		75:25[f]	31.98 (1.14)	4.21 (0.14)	75.2:24.8 (74.9:25.1)
	**18**[g]	racemic	32.06 (0.63)	4.42 (0.22)	50.8:49.2 (50.2:49.8)
	**19**[h]	racemic	32.26 (0.82)	5.19 (0.07)	50.2:49.8 (50.5:49.5)
	**20**[i]	racemic	31.72 (0.30)	4.78 (0.09)	50.2:49.8 (51.0:49.0)
	**21**[j]	racemic	31.97 (0.56)	5.72(0.15)[k]	51.0:49.0 (50.5:49.5)
	**22**[l]	racemic	na[m]	na[m]	na[m]

[a]Average of both signals and (separation between both signals). [b]Average of both signals and (separation between both signals) of the proton on the alpha-carbon of the azide moiety unless otherwise stated. [c]The ratio of the two diastereomers determined by ^{31}P and (^{1}H) NMR integrations. [d]Synthesized according to the procedure described in *Synthesis*, **1990**, 130. [e]Authentic sample synthesized from (-)-menthol via a Mitsanobu transformation. [f]A mixture composed of racemic and pure (-)-isomer in a 1:1 ratio. [g]Synthesized from the reaction of the corresponding iodide with sodium azide in refluxing acetone. [h]Synthesized according to the procedure described in *Synthesis*, **1990**, 130. ^{1}H NMR compared favorably with that reported in *J. Chem. Soc. Perkin Trans. 1*, **1974**, 2287. [i]Synthesized according to the procedure described in *Synthesis*, **1990**, 130. [j]Synthesized according to the procedure described in *J. Am. Chem. Soc.* **1954**, 1231. [k]The average of both signals (and the difference between both signals) of the three benzylic protons in the azaphosphatrane moiety. [l]Synthesized by the PCC oxidation of **21**. The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1994**, *59*, 2902. [m]Deprotonation of **22** gave cation **5** (see Results and Discussion).

Table 2. Crystallographic Data for 5(Cl), 6, and 7

	5(Cl)	**6**	**7**
formula	$C_{30}H_{40}ClN_4P$	$C_{30}H_{39}N_4P$	$C_{30}H_{39}N_4P$
fw	523.08	486.62	502.62
cryst syst	rhombohedral	monoclinic	rhombohedral
space group	*R*3	$P2_1$	*R*3
cryst color, habit	colorless rod	colorless block	colorless block
a, Å	15.7922(10)	9.245(3)	14.5268(10)
b, Å	15.7922(10)	14.7103(8)	14.5268(10)
c, Å	9.8706(6)	10.918(4)	11.3942(18)
V, Å^3	2131.9(2)	1379.3(7)	2082.4(4)
Z	3	2	3
D(calc), g cm^{-3}	1.222	1.172	1.202
temp, K	173(2)	293(2)	296(2)
diffractometer	Bruker CCD-1000	Siemens P4RA	Siemens P4RA
abs correction	empirical (SADABS)	none	semiempirical
radiation	Mo Kα (λ = 0.71073 Å)	Cu Kα (λ = 1.54178 Å)	Cu Kα (λ = 1.54178 Å)
μ, mm^{-1}	0.216	1.058	1.095
θ range, deg	2.54−26.50	2.06−56.54	2.62−56.35
no. of measd reflections	19563	2475	844
no. of obsd reflections	1963	2034	691
R, %[a]	2.26	3.62	3.83
R_w, %[a]	6.16	9.54	10.05
GOF	1.054	1.058	1.030

[a] Quantity minimized = $R(wF^2) = \Sigma[w(F_o^2-F_c^2)]/\Sigma[(wF_o^2)^2]^{1/2}$; $R = \Sigma\Delta/\Sigma(F_o)$, $\Delta = |(F_o-F_c)$.

Table 3. Selected Bond Lengths (Å) and Angles (deg) for 5(Cl)[a]

Bond Distances			
P−N(1)	1.6752(10)	N(1)−C(3)	1.4818(15)
N(1)−C(1)	1.4577(15)	N(2)−C(2)	1.4888(13)
Bond Angles			
N(1)−P−N(1)#2	119.404(10)	C(3)−N(1)−P	121.88(8)
C(1)−N(1)−C(3)	117.04(10)	C(2)#2−N(2)−C(2)	112.54(7)
C(1)−N(1)−P	121.06(8)		

[a] Symmetry transformations used to generated equivalent atoms: #1 −y, x − y, z; #2 −x + y, −x, z.

Table 4. Selected Bond Lengths (Å) and Angles (deg) for 6

Bond Lengths			
P−N(1)	1.694(3)	P−N(2)	1.689(3)
P−N(3)	1.703(3)	N(1)−C(1)	1.455(5)
N(1)−C(7)	1.470(5)	N(2)−C(3)	1.468(4)
N(2)−C(15)	1.476(4)	N(3)−C(5)	1.461(4)
N(3)−C(23)	1.474(4)	N(4)−C(4)	1.437(5)
N(4)−C(2)	1.439(5)	N(4)−C(6)	1.440(5)
Bond Angles			
N(1)−P−N(2)	103.91(14)	N(1)−P−N(3)	104.15(15)
N(2)−P−N(3)	104.42(14)	C(1)−N(1)−C(7)	117.0(3)
C(1)−P−N(3)	125.5(3)	C(7)−N(1)−P	115.5(2)
C(3)−N(2)−C(15)	116.9(3)	C(3)−N(2)−P	125.6(2)
C(15)−N(2)−P	115.9(2)	C(5)−N(3)−C(23)	116.2(3)
C(5)−N(3)−P	124.9(2)	C(23)−N(3)−P	115.5(2)
C(4)−N(4)−C(2)	120.2(4)	C(4)−N(4)−C(6)	119.2(4)
C(2)−N(4)−C(6)	119.8(3)		

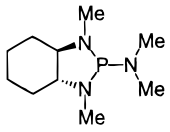
Table 5. Selected Bond Lengths (Å) and Angles (deg) for 7[a]

Bond Lengths			
P−O	1.482(5)	N(1)−C(3)	1.499(5)
P−N(1)	1.654(3)	N(2)−C(2)	1.435(4)
N(1)−C(1)	1.449(5)		
Bond Angles			
N(1)#1−P−N(1)	107.81(12)	N(1)−C(3)-C(4)	112.4(4)
C(1)−N(1)−C(3)	116.0(3)	O−P−N(1)	111.09(12)
C(3)−N(1)−P	119.4(3)	C(1)−N(1)−P	124.4(3)
C(2)−N(2)−C(2)#1	120.0(3)	N(2)−C(2)−C(1)	112.0(4)
N(1)−C(1)−C(2)	114.0(3)	N(1)−C(3)−C(5)	109.0(3)

[a] Symmetry transformations used to generate equivalent atoms: #1 −y, x − 7, z.

of these derivatives were obtained directly without further purification. To evaluate the derivatizing ability of **6**, (±)-neomenthyl azide was reacted with **6** in C_6D_6 at 50 °C for 2 h. Two ^{31}P NMR singlets (32.55 and 31.41 ppm) in a very nearly 1:1 ratio (Table 1) indicated the expected presence of a racemic mixture. ^1H NMR spectra also showed good diastereomeric peak separations for the benzylic proton H_a in the proazaphosphatrane moiety and H_b attached to the α-carbon in the azide moiety (5.65, 5.79 ppm and 4.18, 4.32 ppm, respectively) thus facilitating verification of *ee* values obtained by ^{31}P NMR spectroscopy.

When (−)-neomenthyl azide was reacted under the same conditions, only one singlet was observed at 31.44 ppm in the ^{31}P NMR spectrum and there were two multiplets in the ^1H NMR spectrum (5.65 and 4.32 ppm), corresponding to H_a and H_b, respectively, in **15** thus relating the NMR data to a specific enantiomer. A 1:1 mixture of (±) and (−)-neomenthyl azide employed to test the reliability of this method gave a ratio of (−) to (+) enantiomers from both the ^{31}P and ^1H NMR spectra of very nearly 3:1 as expected. When commercially available chiral phosphorus triamide **16** was used in a parallel reaction for comparison, no diastereomeric differentiation



16

was observed. After reacting **16** with (±)-neomenthyl azide in C_6D_6 at 50 °C for 2 h, only one singlet (30.3 ppm) was observed in the ^{31}P NMR spectrum. Although the corresponding ^1H NMR spectrum indicated some chemical shift separation of the *N*-methyl group protons in moiety **16** of the corresponding diastereomers, the multiplet character of the peaks gave rise to excessive overlap, thus preventing adequate integration. These observations may be attributable to the presence of only two chiral centers in **16,** which apparently do not generate a sufficiently chiral environment around phosphorus in **16** to allow differentiation of the diastereomeric products spectroscopically. In chiral proazaphosphatrane **6** and hence in the iminophosphine product **15**, the three chiral substituents held rigidly by the cage structure probably afford an enhanced chiral phosphorus environment. The azide substrates **17**−**22** used in this work and the results of the NMR measurements on the diastereomeric derivatives are given in Table 1.

In general, the phosphorus imine derivatives examined by decoupled ^{31}P NMR spectroscopy displayed excellent diastereomeric peak separation, allowing accurate integration and quantitative determination of the diastereomeric ratios. ^1H NMR analysis also gave good diastereomeric peak separation, although the spectra were more complex as a result of P−H and H−H coupling, as well as overlap with closely neighboring signals. The advantage of decoupled ^{31}P NMR spectroscopic analysis is that no signals other than the two singlets associated with the diastereomeric derivatives are observed in the spectra. For substrate **22**, however, no evidence for the expected diastereomeric derivatives appeared in the ^{31}P NMR spectrum, and only a peak for cation **5** (−10 ppm) that is characteristic of the protonated form of **6** was observed. This result is attributed to facile deprotonation of the azido carbon, which was confirmed by the disappearance of the NMR spectroscopic resonance of this hydrogen. Both the ^1H and ^{13}C NMR spectra were quite complicated, however, suggesting that side reactions of the anion ensued.

Experimental Section

CH_3CN was dried with CaH_2. THF and Et_2O were dried with sodium, and other solvents were dried with molecular sieves. All solvents were freshly distilled before use, and all reactions were carried out under an Ar atmosphere. The racemic azides used in this work were synthesized by heating NaN_3 with the corresponding bromides in DMF at 60 °C for 24 h. Chemicals employed were purchased from Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed in the Instrument Services Laboratory of the Chemistry Department at Iowa State University.

Synthesis of (*S*,*S*,*S*)-Tris(2-(α)-methylbenzylcarbamoylmethyl)amine (9). Although the synthesis of **9** has been reported,[23] an easier procedure is described here. Nitrilotriacetic acid **8** (19.1 g, 100 mmol) was added to 250 mL of pyridine. The slurry was stirred vigorously while (*S*)-(−)-(α)-methylbenzylamine **4** (37.0 g, 305 mmol) was introduced. The solution was warmed to 50 °C,and $P(OPh)_3$ (99.2 g, 320 mmol) was added. The reaction mixture was kept at 100−105 °C for

10 h, followed by removal of pyridine via vacuum distillation. The resulting yellow oil was dissolved in 600 mL of $CHCl_3$, and then, sequentially, distilled H_2O (3 × 600 mL), 10% aqueous $NaHCO_3$ (10 × 600 mL), distilled H_2O (3 × 600 mL), and brine (2 × 600 mL) were used to wash the organic phase. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, giving the crude product as a pale yellow solid. Recrystallization of the crude product from THF (200 mL) and hexanes (50 mL) at −20 °C for 24 h gave pure **9** as a white solid (42.5 g, 85%). ^1H and ^{13}C NMR data were consistent with those in the literature.[23]

Synthesis of (*S*,*S*,*S*)-Tris(2-(α)-methylbenzylaminoethyl)amine (3). A solution of **9** (10.0 g, 20.0 mmol) in THF (150 mL) was added dropwise at room temperature to a suspension of $LiAlH_4$ (20.0 g, 520 mmol) in THF (300 mL). This mixture was vigorously stirred and heated under reflux for 5 days, after which it was cooled to room temperature. Then 50 mL of 10% aqueous KOH was slowly added, and the resulting mixture was heated under reflux until the salts turned white. After the reaction mixture cooled to room temperature, the salts were removed by filtration. The salts were again heated under reflux for 1 h in a mixture of THF (400 mL) and H_2O (10 mL). After removal of the salts by filtration, the THF layers were combined and concentrated under reduced pressure. The resulting yellow oil was placed in a 20% aqueous KOH (50 mL) solution and extracted with CH_2Cl_2 (2 × 70 mL). After the extract was dried over $MgSO_4$ and concentrated under reduced pressure, **3** was obtained as a pale yellow oil (7.51 g, 82%) that was used in the following reaction without further purification. The sample for characterization was purified by silica gel column chromatography using a mixture of CH_2Cl_2 and MeOH (10:1) as the eluent.

Synthesis of (*S*,*S*,*S*)-Tris(2-(α)-methylbenzylaminoethyl)amine Hydrochloride (3·3HCl). Crude **3** (4.60 g, 10.0 mmol) was placed in a 10% aqueous HCl (50 mL) solution. After the mixture stirred at room temperature for 2 h, CH_2Cl_2 (4 × 50 mL) was used to extract the product. After drying over $MgSO_4$, complete evaporation under reduced pressure, and purification of the residue by silica gel column chromatography using a mixture of CH_2Cl_2 and MeOH (10:1) as the eluent, **3**·3HCl was obtained as a white solid (2.20 g, 48%).

Synthesis of (*S*,*S*,*S*)-Azaphosphatrane (5(Cl)). To a solution of PCl_3 (47.0 mg, 0.33 mmol) in CH_3CN (10 mL) was added $P(NMe_2)_3$ (110 mg, 0.67 mmol) at 0 °C with a syringe. The resulting solution was stirred at 0 °C for 1 h, and then a solution of **3** (458 mg, 1.00 mmol) in CH_3CN (2 mL) was added. After the mixture stirred at room temperature for 12 h, the volatiles were removed under vacuum. The residue was then purified by silica gel column chromatography using a mixture of CH_2Cl_2 and MeOH (15:1) as the eluent, giving **5**(Cl) (330 mg, 62%) as a white solid upon drying over $MgSO_4$ and evaporation under vacuum. A crystal for X-ray analysis was obtained by diffusing Et_2O into a solution of **5**(Cl) in CH_3CN at room temperature for 3 days.

Synthesis of Chiral Proazaphosphatrane (6). A solution of **5**(Cl) (330 mg, 0.63 mmol) in THF (10 mL) was added at room temperature to a suspension of KO-*t*-Bu (125 mg, 1.10 mmol) in THF (20 mL). After the reaction mixture was stirred for 2 h at room temperature, the volatiles were removed in vacuo, and the residue was extracted with benzene (2 × 50 mL). The extract was filtered, and the solvent was removed under vacuum giving **6** as a white solid (250 mg, 82%). A crystal for X-ray analysis was obtained by slow evaporation of a solution of **6** in THF at room temperature.

Synthesis of Chiral Proazaphosphatrane Oxide (7). Bistrimethylsilyl peroxide (180 mg, 1.00 mmol) was added to a solution of **6** (250 mg, 0.51 mmol) in benzene (10 mL) at 0 °C. After standing for 5 h at room temperature, the reaction mixture was filtered, and the solvent was evaporated in a vacuum to give **7** as a white solid (230 mg, 90%). The crystal for X-ray analysis was obtained by dissolving **7** in hot THF, followed by cooling at −20 °C for 24 h.

Crystallographic Structural Determinations of 5(Cl), 6, and 7. The systematic absences in the diffraction data were consistent with space groups *R*3 and $R\bar{3}$ for **5**(Cl) and **7**, respectively, and for space groups $P2_1$ and $P2_1/m$ for **6**. In all cases the *E*-statistics strongly suggested the noncentrosymmetric space groups. The chosen chiral space groups *R*3 for **5**(Cl) and **7** and $P2_1$ for **6** yielded chemically reasonable and computationally stable refinement results. The structures were solved using direct methods that provided locations for most non-hydrogen atoms from the *E*-map.[27] The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. In the case of **5**(Cl) the empirical absorption corrections were based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements.[28] In the case of **7** the semiempirical absorption correction data were collected by the ψ-scan technique. Absorption corrections were not required for **6** because the variations in the integrated ψ-scan intensities were less than 10%. In the structure of **5**(Cl), the cation and anion reside on a 3-fold crystallographic axis that passes through atoms P, N(2), H(0A), and Cl. This structure was refined with a fixed phosphorus−hydrogen distance of 1.400(1) Å. Structures **6** and **7** were refined with soft restraints on thermal displacement parameters to conserve data. Molecule **7** occupies a crystallographic 3-fold axis that passes through atoms P, O, and N(2).

General Procedure for ^1H and ^{31}P NMR Spectral Determination of *ee* Values of Chiral Azides with 6. To an azide (0.05 mmol) in an NMR tube sealed with a rubber septum was added a solution of **6** (29 mg, 0.06 mmol) in C_6D_6 (0.6 mL) at room temperature under an Ar atmosphere. The NMR tube was then heated at 50 °C for 2 h. After the NMR tube cooled to room temperature, the ^{31}P and ^1H NMR spectra were recorded, and the *ee* value of the racemic azide was determined from both NMR peak integrations (Table 1).

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Supporting Information Available: Analytical and spectral data (NMR and mass) for **3**, **3**·HCl, **5**(Cl), **6**, **7**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrich, Bruker Analytical X-ray Systems, Madison, WI).

(28) Blessing, R. *Acta Crystallogr.* **1995**, *A51*, 33.