Reaction of 2,5-bis-TST (3b) with 2-Methylpropanal. A mixture of 2,5-bis-TST (**3b**) (1.15 g, 5 mmol) and the aldehyde (2.27 mL, 25 mmol) was stirred at room temperature for 2 h. The crude reaction mixture was diluted with THF (20 mL) and a solution of TBAF in THF (1 mL) was added. After additional stirring (30 min), the solvent was removed under vacuum and the residue was dissolved in diethyl ether (30 mL). The solution was washed with saturated $NaHCO_3$. Usual workup and chromatography (silica gel, 1:1 diethyl ether–*n*-hexane) gave 0.81 g (80%) of the alcohol **26b**: oil; ^1H NMR δ 0.34 (s, 9 H), 0.94 (d, 3 H, J = 4 Hz), 1.01 (d, 3 H, J = 4 Hz), 2.17 (m, 1 H), 3.24 (d, 1 H), 4.8 (dd, 1 H), 7.66 (s, 1 H).

Anal. Calcd for $C_{10}H_{19}NOSSi$: C, 52.35; H, 8.35; N, 6.10. Found: C, 52.37; H, 8.32; N, 6.11.

Reaction of the Alcohol 26b with 3-Carbomethoxypropionyl Chloride. A mixture of the alcohol **26b** (0.165 g, 0.72 mmol), 3-carbomethoxypropionyl chloride (0.5 mL, 4 mmol), and triethylamine (0.1 mL, 0.72 mmol) was heated at 80 °C for 48 h. The crude mixture was diluted with diethyl ether and washed with saturated $NaHCO_3$. Usual workup and chromatography (silica gel, 1:1 diethyl ether/*n*-hexane) gave 0.166 g (60%) of compound **29**: oil; IR ($CHCl_3$) 1740, 1675 cm^{-1}; ^1H NMR δ 0.98 (d, 6 H, J = 7 Hz), 2.34 (m, 1 H), 2.72 (m, 6 H), 3.24 (m, 2 H), 3.69 (s, 6 H), 5.9 (d, 1 H), 8.3 (s, 1 H); mass spectrum, m/e (relative intensity) M^+ absent, 271 (38), 245 (19), 229 (27), 213 (32), 115 (100).

Anal. Calcd for $C_{17}H_{23}NO_7S$: C, 52.97; H, 6.01; N, 3.63. Found: C, 52.95; H, 6.00; N, 3.64.

Synthesis, Molecular Symmetry, and Chemical Reactivity of *C*-Aryl-Substituted Phosphoraziridines

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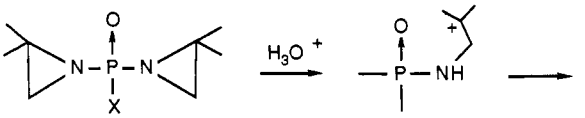
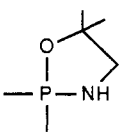
P,P-Bis- and *P,P,P*-tris(1-aziridinyl)phosphoramides containing aryl-substituted aziridine moieties, including para-substituted 2-phenylaziridines, an optically active aziridine, and all the possible *C*-aryl regioisomers of diphenylaziridine were prepared by condensation of the aziridines with the appropriate phosphoryl chlorides. For the preparation of the sterically hindered diphenylaziridine derivatives, an efficient phosphorylation procedure was developed that involved conversion of the aziridines to their lithium salts. The appearance of the aziridine ring regions of the ^1H NMR spectra of these compounds suggested decreased conformational mobility, as well as the presence of an average axis of symmetry in tris(aziridinyl) compounds and a plane of symmetry in certain bis(aziridinyl) systems. The relative reactivities of these new phosphoraziridines with 4-(*p*-nitrobenzyl)pyridine indicate the likelihood of significant S_N1 character in the ring-opening process.

The phosphoraziridines[2] AB-163 (**1a**) and AB-132 (**1b**) have been shown in experimental and clinical studies to be potent antitumor agents as well as radiation sensitizers.[3] Analogues of AB-132 with various alkyl substitution patterns on the aziridine ring have been prepared and considerable variation in both the modes and rates of ring opening by water and 4-(*p*-nitrobenzyl)pyridine (NBP) was observed for these phosphinyl carbamates.[4] The combination of potent antitumor and radiosensitizing activity, as well as the toxic effect of inhibition of acetyl cholinesterase,[5] is exhibited only by compounds such as **1a** and **1b**, which possess geminal dimethyl ring substitution. These properties may be due to a unique mode of hydrolysis involving rapid ring-opening at the substituted position and subsequent ring expansion.[6]



1(a) x = OEt
1(b) x = NHCOOEt



(1)

A pronounced tendency toward ring-opening at the benzylic carbon in *C*-phenyl-substituted aziridines[7] suggests that the corresponding phosphoraziridines might resemble the 2,2-dimethylaziridine series in their chemical reactivity and thereby in their spectrum of biological activity as well. Radiation sensitization by a free radical process would also be expected to be favored. In this report we describe the synthesis of *C*-aryl analogues of the bis(1-aziridinyl) compounds **1** as well as those of tris(2,2-dimethyl-1-aziridinyl)phosphine oxide (TEPA-132),[8] which has geminal dimethyl substitution but lacks the ability of

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(2) Trivial name for class of compounds comprising *N*-phosphinyl derivatives of aziridines.

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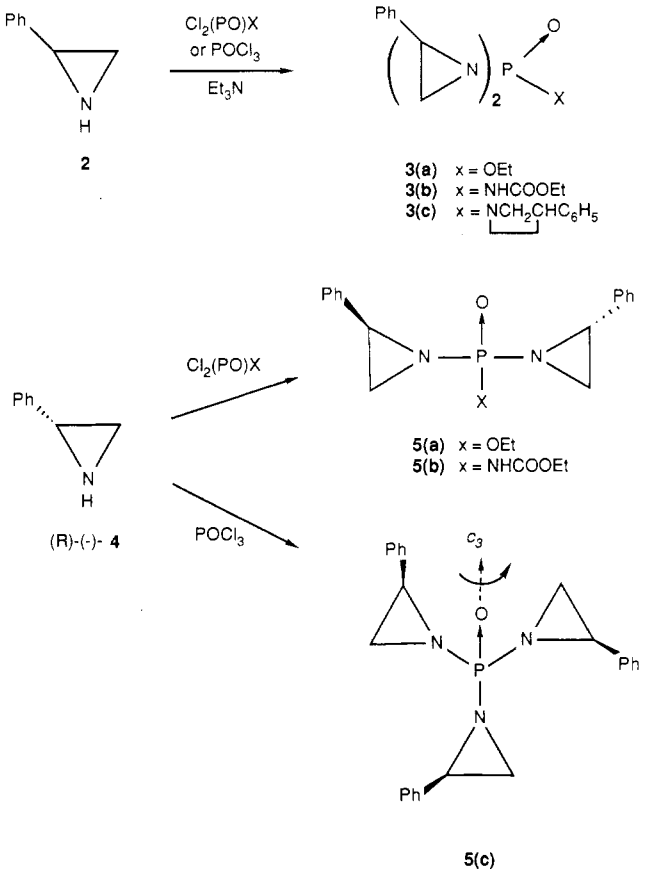
0022-3263/88/1953-1761$01.50/0

Scheme I

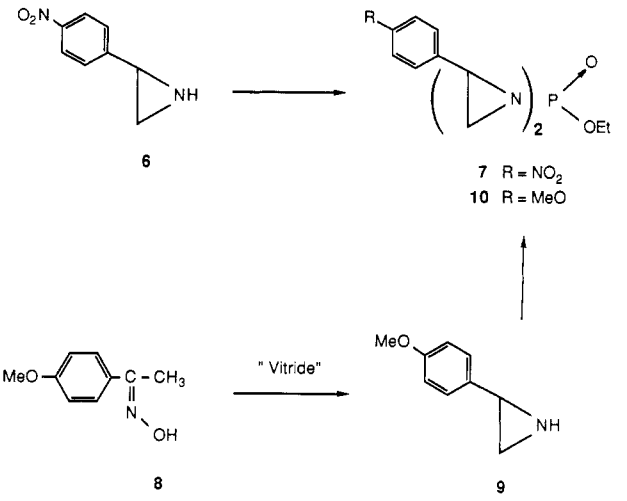


1 to potentiate X-irradiation and to undergo the S_N1-type ring expansion. Para substituents on 2-phenylaziridine and different isomers of diphenylaziridine were employed in order to probe both electronic and steric effects on ring-opening. An efficient procedure for the phosphorylation of hindered aziridines was developed to facilitate the preparation of the diphenylaziridine derivatives.

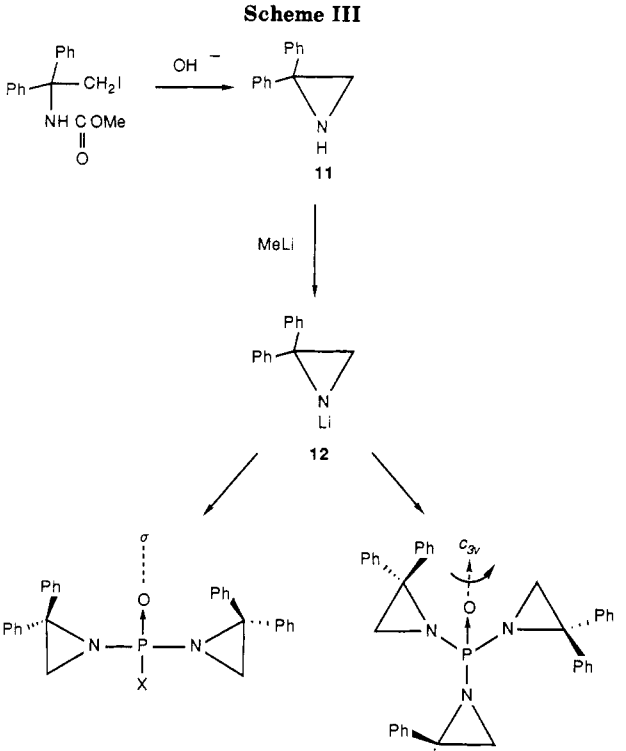
Results and Discussion

2-Phenylaziridine (**2**)[9] was found to react readily with ethyl phosphorodichloridate, ethyl dichlorophosphinyl carbamate, and phosphorus oxychloride in the presence of triethylamine at 0 °C by the methods previously described for *C*-alkylaziridines[4,8,10] to provide the corresponding ester **3a**, carbamate **3b**, and phosphine oxide **3c**, respectively (Scheme I). Compounds **3a–c** exhibited complex proton NMR spectra and were isolated as oils or solids having a broad melting range, suggesting that **3a–c** were obtained as mixtures of diastereomers. In analogy with the symmetry properties of 2,3,4-trihydroxyglutaric acid (ABA-type) described by Eliel,[11] four stereoisomers should be generated by the condensation of two asymmetric aziridines with a molecule of phosphoryl dichloride: a *dl* pair and two meso forms. Condensation of 3 equiv of an asymmetric aziridine with $POCl_3$ should also generate four stereoisomers (as pairs of enantiomers). Since individual diastereomers could not readily be isolated from the mixtures obtained from phosphorylation of racemate **2**, the syntheses were repeated by utilizing (*R*)-(−)-2-phenylaziridine (**4**)[12] to yield the corresponding single diastereomers (*R,R*)-**5a** and -**5b** and *R,R,R* isomer **5c** (Scheme I). They possessed much simpler ^1H NMR spectra than **3a–c**, as it was expected, and all had very large optical rotations, e.g., −321° for **5c**.

Scheme II



Scheme III



2-(*p*-Nitrophenyl)aziridine (**6**) was prepared by epimination of *p*-nitrostyrene[13] with 3,3-pentamethyleneoxaziridine according to the method of Schmitz,[14] and then phosphorylated to yield phosphinate **7** as a diastereomeric mixture (Scheme II). Reduction of *p*-methoxyacetophenone oxime (**8**) with Vitride, based on the general aziridine synthesis of Landor,[15] and careful workup provided the very labile 2-(*p*-methoxyphenyl)aziridine (**9**).

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Table I. 270-MHz ^{1}H NMR Data for N-Phosphorylated Diphenylaziridines (in $CDCl_3$)

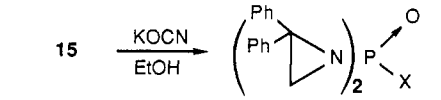
compd	aziridine isomer	3rd group bound to P	chemical shifts, ppm					coupling constants,[b] Hz		
			H_1[a]	H_2[a]	OCH_2	CH_3	Ar	H_1H_2	PH_1	PH_2
13	*gem*	OEt	2.48 (dd)	2.64 (dd)	3.47[d] (quint)	0.88 (t)	7.32 (m)	1.5	13.8	14.8
14	*gem*	aziridine	2.31 (d)				7.21 (s)		13.8	
15	*gem*	Cl	2.85 (dd)	3.09 (dd)			7.29 (m), 7.46 (m)	1.3	16.2	19.5
16	*gem*	NH_2[c]	2.58 (dd)	2.98 (dd)			7.29 (m), 7.41 (m)	1.6	13.3	15.8
23	trans	OEt	3.74 (d)	3.83 (d)	2.87 (m), 3.06 (m) (1:1)	0.56[d] (t)	7.23 (m), 7.32 (m), 7.38 (m)		14.5	15.2
26	cis	OEt	4.10 (d)		4.38[e] (quint)	1.32 (t)	7.11 (m)		16.5	

[a] Protons on aziridine ring. [b] Coupling constants are first-order approximations. [c] δ(NH) 1.80 (br d, J = 3.3 Hz). [d] $J(CH_2-CH_3)$ = 6.9 Hz. [e] $J(CH_2-CH_3)$ = 7.2 Hz.

Condensation with ethyl phosphorodichloridate in the presence of a large excess of Et_3N, followed by chromatography, yielded the less reactive diastereomeric mixture **10**.

The analogous condensation reactions of diphenylaziridines with phosphoryl dichlorides proved to be considerably less facile than those of the monophenyl(aryl)aziridines. 2,2-Diphenylaziridine (**11**) was obtained according to Navada[16] by treatment of methyl *N*-(2-iodo-1,1-diphenylethane)carbamate[17] with methanolic potassium hydroxide (Scheme III). Reaction of **11** with ethyl phosphorodichloridate under the conditions employed for the 2-arylaziridines yielded no product, probably due to severe steric hindrance toward condensation. Use of elevated temperatures yielded only polymeric material. Treatment of **11** at 0 °C with MeLi, followed by ethyl phosphorodichloridate, yielded a complex mixture, as did the use of NaH, while *n*-butyllithium at −78 °C generated the desired product but in variable yields. However, the use of just below 1 equiv of methyllithium per equiv of aziridine at approximately −78 °C in ether solution to generate lithium aziridine **12**, followed by addition of phosphorodichloridate and subsequent stirring at 4 °C, resulted in nearly quantitative precipitation of the desired ethyl bis(2,2-diphenyl-1-aziridinyl)phosphinate (**13**). Tris(aziridinyl)phosphine oxide **14** was obtained in a similar manner by the reaction of phosphorus oxychloride and 4 equiv of aziridine–lithium salt **12**.

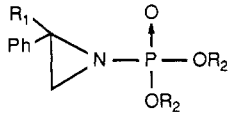
Bis(aziridinyl)phosphinyl carbamate **18** could not be obtained by treatment of the aziridine–lithium salt **12** with ethyl dichlorophosphinyl carbamate, presumably due to competing abstraction of the carbamate N*H* proton. However, bis(2,2-diphenyl-1-aziridinyl)phosphinic chloride (**15**) could be prepared as a fairly stable, crystalline solid by addition of $POCl_3$ to 2 equiv of **12**. The considerable steric bulk of the four benzene rings may be responsible for the much greater stability of **15** than that of the analogous phosphoryl chlorides prepared from ethyleneimine[18] and 2,2-dimethylaziridine.[19] In fact, subsequent reaction of the phosphinic chloride with KOCN in absolute EtOH at 4 °C provided not the phosphinyl carbamate **18** as expected[20,21] but, based on the infrared spectrum, only a phosphinyl isocyanate was generated that was presumably **17**. Heating **17** in situ yielded a carbamate, but attempts at isolation of either **17** or **18** without ring-opening were not successful. However, the phosphinyl chloride **15** could be converted to amide **16** upon treatment with ammonia.



(2)

17 X = NCO
18 X = NHCOOEt

The ^{1}H NMR spectra of bis(2,2-diphenyl-1-aziridinyl)phosphinyl derivatives **13**, **15**, and **16** are all characterized by two apparent doublet-of-doublets for the aziridine ring protons (see Table I for 270-MHz data). The effects of varying field strength and solvent showed that each doublet of doublets is an individual spin system. The spectra of phosphoraziridines of 2,2-dimethylaziridine, such as **1a**,[10] normally have a simple doublet for the aziridine methylene protons (J_{P-H} = 14 Hz). The methylene protons in the corresponding 2,2-diphenylaziridine compounds appear to exhibit geminal coupling, perhaps due to hindrance to aziridine N-inversion or P–N rotation. N-Invertomers were first observed in NMR spectra of secondary amines by Bardos and co-workers in the case of 2,2,3,3-tetramethylaziridine[22] and have also been reported for diphenylaziridines.[23,24] The aziridine portion of the spectrum of tris(aziridinyl) compound **14** consists only of a doublet, however, as does that reported for the monoaziridinylphosphinate **19**.[25] The equivalence of the aziridine rings indicated in the spectrum of **14** may be the result of an average axis of rotational symmetry. The lack of geminal coupling appears to indicate that in addition a plane of symmetry passes through each aziridine ring to yield average C_{3v} symmetry. Thus, in **14** corresponding protons in different rings would be homotopic and those in the same ring enantiotopic, while in **13**, **15**, and **16** protons in different rings would be enantiotopic (due to a plane of symmetry through P=O) and those in the same ring diastereotopic (see Scheme III).



19 R_1 = Ph, R_2 = Me
20 R_1 = H, R_2 = Et

(3)

In the case of the 2-phenylaziridine derivatives, the aziridine proton pattern in the spectrum of **5c** is nearly identical with that of the monoaziridinyl analogue **20**,[26] while **5a** and **5b** possess much more complex spectra. Thus

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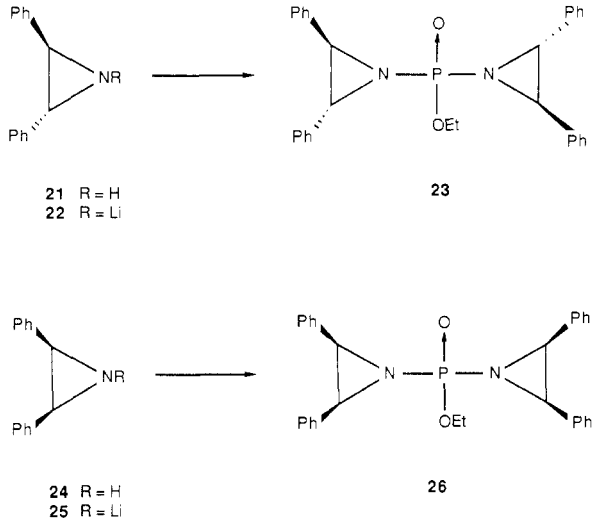
Scheme IV



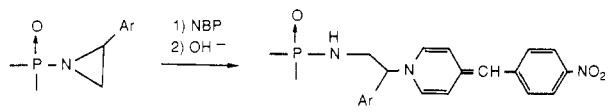
5c may also have average C_3 symmetry that allows the aziridine rings to be equivalent, while 5a and 5b lack an axis or plane of symmetry resulting in nonequivalent aziridine rings.

It was found that *trans*-[25] and *cis*-2,3-diphenylaziridine[27] (21 and 24, respectively) could also be converted to their corresponding lithium salts (22, 25) by reaction with MeLi at −78 °C (Scheme IV). Subsequent treatment with ethyl phosphorodichloridate yielded the corresponding crystalline phosphoraziridines 23 and 26. As 23 was generated from a chiral aziridine, a *dl*-pair and two meso isomers can in principle be formed. The ^{1}H NMR spectrum of the analytically pure, crystalline product 23 indicates that it consists of a single diastereomer. Variation of the field strength revealed that the two doublets for the aziridine ring protons in 23 are due to independent spin systems. As with 5a and 5b this compound appears to lack a plane of symmetry and hence is probably the *dl*-form (shown in Scheme IV), with the trans protons being homotopic in this instance due to the possibility of exchange by 180° P–N rotation. Cis isomer 26 has a plane of symmetry that results in equivalent aziridine rings and a simpler spectrum. The lack of symmetry in 23 is also supported by the presence of two sets of multiplets for the methylene group in the ethyl ester moiety, while single quintets are observed in the cases of 13 and 26.

The preparation of 13–16, 23, and 26 described above demonstrates the utility of using lithium salts for N-derivatization of diphenylaziridines. The generation of lithium aziridines 12, 22, and 25 has been reported by Kauffmann[28] but always with subsequent thermal ring-opening to yield 2-azaallyllithium species that are of utility in 1,3-anionic cycloadditions. The intact aziridine amide, although presumed to be the intermediate in the formation of such 1,3-anions, was not trapped as was the case here.

In order to probe steric and electronic effects of aromatic substituents on the ring-opening behavior of phosphoraziridines, relative initial rates of reaction (k')[31] with 4-(*p*-nitrobenzyl)pyridine (NBP)[29-31] in aqueous ethanol (80 °C, pH 4.0) were determined. The plots of absorbance of the colored adduct formed with NBP (after addition of alkali) vs time of incubation were almost all nonlinear, presumably due to competing hydrolysis of the aziridine or the adduct. For the monophenyl phosphoraziridines 3a–c rates of between 0.5 and 1.7 ($\times 10^{-3}$ min^{-1}) were obtained, in contrast with 5 to 10 times higher rates for the 2,2-dimethyl-substituted compounds 1a,b and tris(2,2-dimethyl-1-aziridinyl)phosphine oxide. Among the diphenyl phosphoraziridines, only the trans isomer 23 yielded significant adduct ($k' = 0.68$). These results tend to indicate decreasing alkylating activity with increasing steric bulk.

Scheme V



The initial rates of reaction with NBP for the *p*-methoxy-substituted (10), unsubstituted (3a), and *p*-nitro-substituted (7) (2-phenyl-1-aziridinyl)phosphinates are 3.9, 1.55 and 1.1, respectively. The increase in rate with increased electron donation by the aromatic moiety could be due to enhancement of protonation of the aziridine nitrogen or may be a result of stabilization of an incipient carbonium ion. Acid-catalyzed ring-opening at the substituted carbon has been observed for dimethyl (2-phenyl-1-aziridinyl)phosphinate and the free aziridines 2 and 9.[12,32] Adduct formation between NBP and N-phosphorylated 2-arylaziridines by an S_N1-type process thus seems likely and is depicted in Scheme V.

The rates of reaction of the free diphenylaziridines were measured and found to be consistent with those of the corresponding phosphoraziridines: 4.0 for trans isomer 21, 0.7 for cis isomer 24, and no significant yield of adduct for *gem* isomer 11. The products of the ring-opening of diphenylaziridines with HF[33,34] and HCl[7] typically exhibit a predominance of an S_N1 mechanism. The slower cleavage of 24 than 21 by HF/pyridine[33] is proposed by Wade to be the result of steric hindrance interfering with resonance stabilization of any positive charge in 24. Although a lower rate of reaction with HF for 11 than for 21 was not observed by Wade, steric hindrance to resonance may be responsible for the lack of reaction of the geminally substituted aziridine with NBP. The relatively rapid ring-opening of phosphoraziridine 23 compared to 13 and 26 may be the result of a similar dependence on steric interactions.

The relative rates of ring-opening by 4-(*p*-nitrobenzyl)pyridine within each series of aromatic phosphoraziridines thus appear to be consistent with significant S_N1 character in these processes, which may be desirable for biological activity considering the apparent activation of the radiosensitizers 1a and 1b by S_N1-type ring-opening. Evaluation of these new compounds as radiation sensitizers and antitumor agents is in progress.

Experimental Section

Melting points were determined in an open capillary tube in a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 197 spectrophotometer calibrated with polystyrene film. Nuclear magnetic resonance spectra were

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recorded on a Varian T-60 or a JEOL FX 270 spectrophotometer. Tetramethylsilane was used as an internal standard. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter at the sodium D line. Thin-layer chromatography was performed on Analtech silica gel GF Uniplates, or Eastman plastic sheets if so indicated, and components were visualized with short wavelength ultraviolet light or iodine vapor. Preparative chromatography was carried out on 20 cm × 20 cm plates coated with a 2-mm layer of Machery-Nagel silica gel P/UV$_{254}$, unless otherwise indicated. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, or by Galbraith Laboratories, Inc., Knoxville, TN.

Methyllithium in ether (Alfa) was titrated by the method of Duhamel[35] just prior to use. All reactions involving its use were performed in flame-dried glassware, under a dry nitrogen atmosphere and by utilizing anhydrous, reagent-grade ether stored over sodium metal. Ethyl phosphorodichloridate was purchased from Aldrich Chemical Co. and redistilled before use. In all procedures involving phosphoraziridines, anhydrous, reagent-grade solvents were employed. THF was distilled from $LiAlH_4$, toluene and benzene were distilled from CaH_2, and methylene chloride was distilled from P_2O_5.

Ethyl Bis(2-phenyl-1-aziridinyl)phosphinate (3a). A solution of 2-phenylaziridine (**2**)[9] (2.00 g, 0.017 mol) and Et_3N (2.3 mL, 0.017 mol) in ether (50 mL) was cooled to 0 °C. Ethyl phosphorodichloridate (1.22 g, 0.0075 mol) in ether (25 mL) was then added dropwise with stirring over 30 min at 0 to −3 °C. Stirring was continued for another 24 h at 4 °C, the suspension was filtered, and the residual powder (Et_3N·HCl) was washed with cold ether. Flash evaporation of the filtrate and washings yielded a clear, colorless, viscous oil, which was subsequently subjected to high vacuum and heated at 45–70 °C for 5 h to provide 1.75 g (71%) of an oil. Purification with a micromolecular distillation apparatus at 0.02–0.04 mm (100–145 °C bath temperature) and subsequent drying at 60–100 °C (0.005–0.001 mm) for 54 h yielded 0.973 g (40%) of **3a** as a colorless oil: IR (neat) 3475 (H_2O), 1225 (azir. (aziridine), P=O), 1040 (C–O), 930 (P–N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20 and 1.28 (2 t, 3 H, CH_3's of diastereomers, J = 7 Hz), 2.15, (dm, 2 H, azir. H-3 cis to Ph, J = 18 Hz), 2.72 (dm, 2 H, azir. H-3 trans to Ph, J_{PH} = 16 Hz), 3.53 (dm, 2 H, azir. H-2, J = 14 Hz), 4.22 (m, 2 H, CH_2O), 7.22 (m, 10 H, Ar). Anal. Calcd for $C_{18}H_{21}N_2O_2P \cdot {}^1/_4\ H_2O$: C, 64.95; H, 6.51; N, 8.42; P, 9.30. Found: C, 64.99; H, 6.65; N, 8.40; P, 9.69.

Ethyl Bis(2-phenyl-1-aziridinyl)phosphinylcarbamate (3b). Phosphorisocyanatidic dichloride[36] (1.60 g, 0.01 mol) in toluene (25 mL) was cooled to 0–3 °C, whereupon absolute EtOH (0.58 mL, 0.01 mol) in toluene (5 mL) was added dropwise with stirring over 40 min at this temperature. Stirring was continued for another 2 h at room temperature. The resulting solution of ethyl dichlorophosphinylcarbamate[36] was immediately added dropwise with stirring to a solution of 2-phenylaziridine (**2**)[9] (2.50 g, 0.0212 mol) and Et_3N (2.95 mL, 0.0212 mol) in toluene (20 mL) over 1 h at 0–2 °C. After the mixture was stirred for 24 h at 4 °C, the resulting precipitate was filtered and washed with toluene. The filtrate and washings were evaporated in vacuo to a colorless glass, which was dissolved in warm ether (25 mL) and cooled to yield 2.85 g (78%) of **3b** as a white amorphous solid (mp 90–107 °C) that was pure by NMR. Trituration with ether (50 mL) and then warm ether (35 mL) and repeated recrystallization (THF/hexanes) afforded 0.107 g white needles, mp 107.5–110.5 °C, which served as an analytical sample: IR ($CHCl_3$) 3400 (NH), 1740 (C=O), 1240 (P=O), 1080 (C–N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 and 1.17 (2 t, 3 H, CH_3's of 2 diastereomers, J = 7 Hz), 2.32 (dm, 2 H, azir. H-3 cis to Ph, J_{PH} = 15 Hz), 2.90 (ddm, 2 H, azir. H-3 trans to Ph, J_{PH} = 18, J(cis) = 6 Hz), 3.75 (dm, 2 H, azir. H-2), 4.07 and 4.13 (2 q, 2 H, CH_2O, J = 7 Hz), 6.90 (m, 1 H, NH), 7.32 (m, 10 H, Ar). Anal. Calcd for $C_{19}H_{22}N_3O_3P$: C, 61.45; H, 5.97; N, 11.31. Found: C, 61.43; H, 6.01; N, 11.55.

Tris(2-phenyl-1-aziridinyl)phosphine Oxide (3c). A solution of $POCl_3$ (1.23 g, 0.0080 mol) in toluene (25 mL) was added dropwise over 20 min to **2**[9] (2.94 g, 0.0248 mol) and Et_3N (3.45 mL, 0.0248 mol) in toluene (35 mL) at 0–5 °C with stirring. After being stirred at 4 °C for 38 h, the suspension was evaporated to dryness and the residue extracted with hexane. Evaporation of the hexane extract yielded a white powder, which after three recrystallizations (ether) afforded 0.451 g (14%) of **3c**[37] as fine needles: mp 85.5–88 °C; IR ($CHCl_3$) 1245–1200 (azir., P=O), 935 (P–N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.20 (dm, 3 H, azir. H-3 cis to Ph, J_{PH} = 13 Hz), 2.75 (m, 3 H, azir. H-3 trans to Ph), 3.58 (m, 3 H, azir. H-2), 7.23 (m, 15 H, Ar). Anal. Calcd for $C_{24}H_{24}N_3OP$: C, 71.81; H, 6.03; N, 10.47. Found: 71.70; H, 6.06; N, 10.47.

(*R*)-2-Phenylaziridine (4).[12] Ring closure by the method of Nabeya[12] yielded a crude oil that contained about 5% acetophenone by ^{1}H NMR. Fractional distillation provided **4** as a colorless oil (31%): $[\alpha]^{26}_D$ −45.98° (*c* 9.835, EtOH) (lit.[12] $[\alpha]^{26}_D$ −43.4° (*c* 10.062, EtOH); ^{1}H NMR ($CDCl_3$) identical with that of the racemic compound,[9] except for a signal at δ 2.55 (s, CH_3CO), indicating ca. 0.3% of acetophenone in product.

(*R*,*R*)-Ethyl Bis(2-phenyl-1-aziridinyl)phosphinate (5a). The procedure described for the synthesis of **3a** was followed, in this case using **4** (1.88 g, 0.0160 mol) instead of **2**. The oil obtained was not distilled as before but instead was dissolved in ether/petroleum ether (1:1) and a trace of insoluble solid was filtered. Reevaporation of the solvent and storage of the oil at −12 °C for 2 days afforded, after drying at high vacuum, **5a** as a semicrystalline solid (quantitative yield), which could not be recrystallized from a variety of solvent systems: mp 25–38 °C; $[\alpha]^{26}_D$ −220° (*c* 1.20, absolute EtOH); IR (neat) identical with that of **3a**; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, CH_3, J = 7 Hz), 2.17 (dm, 2 H, azir. H-3 cis to Ph, J_{PH} = 14 Hz), 2.72 (dm, 2 H, azir. H-3 trans to Ph, J_{PH} = 18 Hz), 3.49 (dm, 2 H, azir. H-2, J_{PH} = 14 Hz), 4.22 (d q (apparent quint), 2 H, CH_2O, J_{PH} = J_{HH} = 7 Hz), 7.22 (s, 10 H, Ar). Anal. Calcd for $C_{18}H_{21}N_2O_2P \cdot {}^1/_4\ H_2O$: C, 64.95; H, 6.51; N, 8.42. Found: C, 64.59; H, 6.70; N, 8.85.

(*R*,*R*)-Ethyl Bis(2-phenyl-1-aziridinyl)phosphinylcarbamate (5b). The procedure for the synthesis of **3b** was followed, except that the aziridine used here was **4** instead of **2**. After filtration of the Et_3N·HCl, the resulting solution was evaporated at reduced pressure, and the residue was crystallized (THF/hexanes) to provide 3.17 g of **5b** as fine crystals (85%): mp 101–111 °C; $[\alpha]^{26}_D$ −225° (c 0.515, absolute EtOH); IR nearly identical with that of **3b**; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3 H, CH_3, J = 7 Hz), 2.23 (dm, 2 H, azir. H-3 cis to Ph, J_{PH} = 15 Hz), 2.88 (ddd, 2 H, azir. H-3 trans to Ph, J_{PH} = 18 Hz, J(cis) = 6 Hz, J(*gem*) = 2 Hz), 3.66 (dm, 2 H, azir. H-2), 4.08 (q, 2 H, CH_2O, J = 7 Hz), 7.20 and 7.25 (2 s, 10 H, Ar), 7.67 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{22}N_3O_3P$: C, 61.45; H, 5.97; N, 11.31. Found: C, 61.47; H, 5.97; N, 11.31.

(*R*,*R*,*R*)-Tris(2-phenyl-1-aziridinyl)phosphine Oxide (5c). The procedure for the synthesis of **3c** was followed, except that the aziridine used here was **4** instead of **2**. The precipitated powder was filtered and washed with toluene and then ether. The combined filtrates were evaporated, dissolved in toluene, filtered, and reevaporated. The residue was crystallized from ether/petroleum ether and then recrystallized from ether to afford 1.56 g of **5c** as large, white needles (48%): mp 81–83 °C; $[\alpha]_D^{26}$ −321° (*c* 1.35, absolute EtOH); IR nearly identical with that of **3c**; ^{1}H NMR ($CDCl_3$) δ 2.19 (ddd, 3 H, azir. H-3 cis to Ph, J_{PH} = 16 Hz, J(trans) = 3 Hz, J(*gem*) = 1.5 Hz), 2.80 (ddd, 3 H, azir. H-3 trans to Ph, J_{PH} = 17 Hz, J(cis) = 6 Hz), 3.49 (ddd, 3 H, azir. H-2, J_{PH} = 15 Hz), 7.22 (s, 15 H, Ar). Anal. Calcd for $C_{24}H_{24}N_3OP$: C, 71.81; H, 6.03; N, 10.47. Found: C, 71.78; H, 6.04; N, 10.43.

Ethyl Bis(2-(*p*-nitrophenyl)-1-aziridinyl)phosphinate (7). Ethyl phosphorodichloridate (0.407 g, 2.5 mmol) in toluene (5 mL) was added dropwise to 2-(*p*-nitrophenyl)aziridine (**6**)[14] (0.816 g, 5.0 mmol) and Et_3N (0.725 mL, 5.2 mmol) in toluene (20 mL) at −2 °C with stirring. The suspension was then stirred at 4 °C for 24 h and then at room temperature for 5 h. The precipitate was removed by filtration and washed with toluene (40 mL), and the filtrates and washings were evaporated at reduced pressure. Purification on preparative silica gel plates developed with THF and extracted with 1,2-dichloroethane/MeOH (5:1) afforded an oil. Crystallization by trituration with ether and recrystallization

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(THF/hexanes) gave 0.492 g (47%) of **7** as a powder: mp 115 °C dec; IR ($CHCl_3$) 1525 [$\nu(NO_2)$ asym], 1325 [$\nu(NO_2)$, sym], 1260–1200 (P=O, azir.), 1040 (C–O), 930 (P–N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 and 1.37 (2 t, 3 H, CH_3 of diastereomers, J = 7 Hz), 2.25 (dm, 2 H, azir. H-3 cis to Ph, J_{PH} = 14 Hz), 2.87 (dm, 2 H, azir. H-3 trans to Ph, J_{PH} = 17 Hz), 3.66 (dm, 2 H, azir. H-2), 4.25 and 4.32 (2 quint., 2 H, CH_2O of diastereomers, $J_{PH} = J_{HH}$ = 7 Hz), 7.45 (m, 4 H, H_o), 8.17 (m, 4 H, H_m). Anal. Calcd for $C_{18}H_{19}N_4O_6P$: C, 51.68; H, 4.58; N, 13.39. Found: C, 51.99; H, 4.40; N, 13.40.

2-(*p*-Methoxyphenyl)aziridine (9). The method reported for the synthesis of *p*-nitroacetophenone[38] was utilized to prepare *p*-methoxyacetophenone oxime **8** in 97% yield as white crystals (stored in a desiccator in the cold): mp 84–88.5 °C (lit.[39] mp 86 °C); ^1H NMR ($CDCl_3$) δ 2.27 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3O), 6.85 (dm, 2 H, H_m), 7.52 (dm, 2 H, H_o).

A solution of **8** (8.25 g, 0.05 mol) in dry THF (25 mL) was added dropwise under N_2 to a stirred solution of sodium dihydridobis(2-methoxyethoxy)aluminate (Vitride, 0.15 mol, 70% solution in toluene, Alfa) in THF (200 mL) at reflux over 60 min. After being boiled further (2 h), the solution was allowed to cool to room temperature (2 h), and then 2 N NaOH (25 mL) was added dropwise (1 h) with vigorous stirring. The solution was decanted from gummy precipitate, which then was washed with ether (150 mL). The combined solutions were dried over anhydrous Na_2SO_4 at 4 °C and filtered, and the Na_2SO_4 was washed with dry toluene. The combined filtrates and washings were evaporated at reduced pressure at 30 °C and then chromatographed on a dry-packed column of neutral alumina (700 g, Woelm dry column grade with fluorescent indicator, Activity Grade III), in a Nylon tube. The column was developed with dry ether/Et_3N (10:1), and the section from just above the origin to the beginning of the fast-migrating, short-UV-absorbing band was excised. The boundaries of the aziridine-containing region were confirmed by the production of a violet color upon treatment of samples with (*p*-nitrobenzyl)-pyridine spray reagent.[40] The band was extracted with CH_2Cl_2/MeOH/Et_3N (12:4:1, 1 L) and the extract evaporated at 30 °C to yield a yellow oil (4.91 g). Treatment with dry toluene (2 mL) and fractional distillation (66 °C (0.02 mm), 85–120 °C bath) afforded a colorless oil (1.54 g) that was approximately 93% **9** by ^1H NMR (yield of **9** = 19%). The only significant impurity appeared to be 1-(*p*-methoxyphenyl)ethylamine: TLC (ether with 5% Et_3N) R_f 0.29 (primary amine) and 0.38 (**9**); ^1H NMR ($CDCl_3$) δ 0.72 (br s, 1 H, NH), 1.35 (d, 0.22 H, CH_3CNH_2, J = 7 Hz), 1.72 (d, 1 H, azir. H-3 cis to Ph, J(trans) = 3 Hz), 2.12 (d, 1 H, azir. H-3 trans to Ph, J(cis) = 6 Hz), 2.95 (dd, 1 H, azir. H-2), 3.82 (s, 3 H, CH_3O), 4.07 (q, 0.07 H, $CHNH_2$, J = 7 Hz), 6.83 (dm, 2.12 H, H_m, $J_{o,m}$ = 9 Hz), 7.14 and 7.17 (2 dm, 2.56 H, H_o of azir. (downfield) and amine). The spectral data are consistent with those of a previous preparation.[32b]

In an attempt to obtain an analytical sample, 0.5 g of the above oil was applied to silica gel plates, which were developed with THF (5% Et_3N) and extracted with $ClCH_2CH_2Cl$/MeOH/Et_3N (20:2:1). Evaporation of the extracts yielded a yellow oil (0.255 g) that was free of primary amine byproduct by NMR but 40% decomposed. Complete decomposition resulted when vacuum distillation of this material was attempted.

Ethyl Bis(2-(*p*-methoxyphenyl)-1-aziridinyl)phosphinate (10). Ethyl phosphorodichloridate (0.489 g, 3.0 mmol) in toluene (10 mL) was added dropwise over 45 min to **9** (0.960 g, 6.04 mmol by ^1H NMR) and Et_3N (4.18 mL, 30.0 mmol) in toluene (20 mL) at −4 to −2 °C. After being stirred for 5 h at 4 °C, the suspension was allowed to reach room temperature and filtered and the residual powder washed with toluene (15 mL). The filtrate and washings were evaporated and then chromatographed on silica gel plates developed with dry THF/Et_3N (10:1), and the product was extracted with freshly distilled 1,2-dimethoxyethane. The solvent was removed in vacuo and again evaporated after each treatment with 1,2-dichloroethane (2×) and CH_2Cl_2 (3×). Subsequent drying at high vacuum at 30 °C afforded 0.846 g (70%) of **10** as a viscous oil. The analytical sample was obtained by drying at high vacuum at 40 °C over P_2O_5. There was no indication of the presence of significant byproducts in the final product in spectra or chromatographically: IR (neat) 3400 (H_2O), 1250–1225 (P=O), 1035 (C–O), 930 (P–N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (m, 3 H, CH_3C), 2.17 (dm, 2 H, azir. H-3 cis to Ph, J_{PH} = 14 Hz), 2.70 (dm, 2 H, azir. H-3 trans to Ph, J_{PH} = 14 Hz), 3.45 (dm, 2 H, azir. H-2), 3.78 (s, 6 H, CH_3O), 4.23 (m, 2 H, CH_2O), 6.86 (m, 4 H, H_m), 7.21 (m, 4 H, H_o). Anal. Calcd for $C_{20}H_{25}N_2O_4P \cdot {}^1/_2H_2O$: C, 60.44; H, 6.59; N, 7.05. Found: C, 60.25; H, 6.65; N, 7.05.

2,2-Diphenylaziridine (11).[16] Methyl *N*-(2-iodo-1,1-diphenylethane)carbamate[17] (25.4 g, 0.069 mol) in methanolic KOH (37 g in 400 mL MeOH) was boiled for 2 h. The suspension was filtered and the filtrate concentrated to 200 mL in vacuo and poured into water (500 mL), and the resulting suspension was extracted with ether. The organic extracts were washed well with water, dried (Na_2SO_4), and evaporated. The oil was dried over NaOH pellets and distilled to provide 8.68 g (67%) of **11** as a colorless oil: bp 111–115 °C (0.17 mm); IR (neat) 3300 (NH), 1605, 1495 (Ar), 1450 (azir. CH bend) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (br s, 1 H, NH), 2.38 (s, 2 H, CH_2), 7.30 (s, 10 H, Ar). Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.18; H, 6.85; N, 7.41.

Ethyl Bis(2,2-diphenyl-1-aziridinyl)phosphinate (13). Methyllithium (12 mmol, 1.39 M in ether) was added dropwise over 30 min to a stirred solution of **11** (2.34 g, 12.2 mmol) in ether (100 mL) at approximately −78 °C (CO_2/acetone), and the clear, colorless solution stirred for an additional 60 min at this temperature. To the solution of lithium amide **12** was then added over 3 min a solution of ethyl phosphorodichloridate (0.978 g, 6.0 mmol) in ether (5 mL). After being stirred for 24 h at 4 °C, the suspension was filtered and the residual white powder washed with ether. The filtrate was evaporated to an oil and dissolved in CH_2Cl_2 and the turbid solution stored in the cold for several days. After repeated filtrations through Celite-545 to remove all of the suspended LiCl, the now clear solution was evaporated and crystallized from ether to afford 2.44 g (85%) of **13** as fine white crystals: mp 147 °C dec; IR ($CHCl_3$) 1240 (P=O), 1025 (C–O), 980 (P–N) cm^{-1}. Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 74.98; H, 6.08; N, 5.83. Found: C, 75.39; H, 5.96; N, 5.85.

Tris(2,2-diphenyl-1-aziridinyl)phosphine Oxide (14). To a stirred solution of **12** (12 mmol, prepared as described for **13**) in ether (50 mL) at −78 °C was added over 5 min $POCl_3$ (0.460 g, 3.0 mmol) in ether (5 mL). After being stirred for 38 h at 4 °C, the thick suspension was filtered and the residual powder washed thoroughly with ether (75 mL) and then extracted with CH_2Cl_2 (50 mL). The turbid CH_2Cl_2 solution was filtered through Celite-545, evaporated, and then coevaporated several times with ether to yield white crystals, which were recrystallized (CH_2Cl_2/ether) to provide 1.61 g (85%) of **14**: mp 140 °C dec; IR ($CHCl_3$) 3370 (H_2O), 1210 (P=O), 980 (P–N) cm^{-1}. Anal. Calcd for $C_{42}H_{36}N_3OP \cdot {}^1/_4H_2O$: C, 79.54; H, 5.72; N, 6.62. Found: C, 79.67; H, 5.90; N, 6.77.

Bis(2,2-diphenyl-1-aziridinyl)phosphinic Chloride (15). To a solution of **12** (20 mmol, prepared as described for the synthesis of **13**) in ether (200 mL) at −78 °C was added over 5 min a solution of $POCl_3$ (1.53 g, 10.0 mmol) in ether (5 mL). After being stirred for 64 h at 4 °C, the suspension was filtered and the residual white powder washed with cold ether (50 mL). It was then extracted with CH_2Cl_2 (150 mL), and the extract was filtered through Celite-545, treated with benzene (20 mL), and evaporated. The foam was dissolved in CH_2Cl_2 (25 mL), and ether (50 mL) and then petroleum ether (25 mL) were added to yield upon cooling 2.98 g (63%) of **15** as off-white crystals (mp 139 °C dec), which was homogeneous on TLC. Recrystallization provided the analytical sample: mp 146 °C dec; IR ($CHCl_3$) 3450 (H_2O), 1255 (P=O), 980 (P–N) cm^{-1}. Anal. Calcd for $C_{28}H_{24}ClN_2OP \cdot {}^1/_3H_2O$: C, 70.51; H, 5.21; N, 5.87; Cl, 7.43. Found: C, 70.64; H, 5.22; N, 5.88; Cl, 7.42.

Bis(2,2-diphenyl-1-aziridinyl)phosphinic Amide (16). Anhydrous NH_3 was passed through a stirred solution of **15** (0.500 g, 1.06 mmol) in THF (25 mL) for 6 h and then above it (3 h) at 0 °C. The thick suspension was allowed to sit overnight at 4 °C and was then filtered and the residual solid washed with CH_2Cl_2 (10 mL). The combined filtrate and washings were

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evaporated in vacuo to a powder, which upon recrystallization (hot THF/hexanes) afforded 0.311 g (65%) of **16** as a white powder: mp 135 °C dec; IR (KBr) 3440 (NH_2 str. asym.), 3210 (NH_2 str. sym.), 1555 (NH bend), 1215 (P=O), 975 (P–NR_2) cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_3OP$: C, 74.48; H, 5.80; N, 9.31. Found: C, 74.45; H, 5.82; N, 9.31.

***trans*-2,3-Diphenylaziridine (21).** Dimethyl (*trans*-2,3-diphenyl-1-aziridinyl)phosphinate[25] was prepared by the reported method as a white powder: ^1H NMR ($CDCl_3$) δ 3.45 and 3.52 (2 d, 6 H, nonequivalent CH_3's, J_{PH} = 11 Hz), 3.86 (d, 2 H, azir. CH–CH, J_{PH} = 15 Hz), 7.35 (m, 10 H, Ar).

Following the method outlined by Hassner[25] for the preparation of crude **21**, a solution of the above powder (9.77 g, 0.032 mol) in anhydrous ether (225 mL) was added dropwise over 25 min to $LiAlH_4$ (0.083 mol) in ether (25 mL). After the mixture was stirred at room temperature for 2 h, water (3 mL), 15% NaOH solution (3 mL), and water (5 mL) were added successively to the reaction mixture over 3 h with stirring. The resulting gray powder was filtered and washed with ether (600 mL, last half warm), and the filtrate and washings were evaporated to yield a solid at high vacuum (4.41 g). Recrystallization (*n*-pentane) provided 3.74 g (60%) of **21** as white crystals: mp 51–52 °C (lit.[41] mp 46–47 °C); IR ($CHCl_3$) 3320 (NH str.), 1450 (azir. CH bend) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 1 H, NH), 3.07 (s, 2 H, azir. CH–CH), 7.28 (s, 10 H, Ar). Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.02; H, 6.72; N, 7.14.

Ethyl Bis(*trans*-2,3-diphenyl-1-aziridinyl)phosphinate (23). Methyllithium (4.0 mmol, 1.87 M in ether) was added dropwise over 5 min to a stirred solution of **21** (0.800 g, 4.1 mmol) in ether (50 mL) at approximately −78 °C (CO_2/acetone) with stirring. The white suspension was stirred at this temperature for another 60 min. Ethyl phosphorodichloridate (0.326 g, 2.0 mmol) in ether (2 mL) was then added to the suspension of lithium salt **22** over 5 min. The temperature was allowed to rise to −25 °C (CO_2/CCl_4), whereupon the salt dissolved. After being stirred for another 45 min at this temperature and then at 4 °C for 36 h, the thick white suspension was filtered cold. The residual powder was washed with cold ether (15 mL) and then extracted with CH_2Cl_2 (2 × 15 mL). The CH_2Cl_2 solutions were filtered through Celite-545 and evaporated to dryness. Recrystallization (acetone) provided 0.239 g of **23** as analytically pure rhombic crystals (mp 151–156.5 °C). The ether filtrate was evaporated, dissolved in CH_2Cl_2, and filtered through Celite. Evaporation and crystallization (ether) yielded additional crystalline product (mp 146–154 °C) (total 39%): IR ($CHCl_3$) 1230–1210 (P=O), 1030 (d, C–O), 960 (P–N) cm^{-1}. Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 74.98; H, 6.08; N, 5.83. Found: C, 75.05; H, 6.09; N, 5.82.

Ethyl Bis(*cis*-2,3-diphenyl-1-aziridinyl)phosphinate (26). Methyllithium (6.0 mmol, 1.90 M in ether) was added dropwise over 10 min to a stirred suspension of *cis*-2,3-diphenylaziridine (**24**)[27] (1.20 g, 6.15 mmol) in ether (75 mL) at approximately −78 °C (CO_2/acetone), with complete dissolution of the aziridine. After being stirred at this temperature for 75 min, the yellow solution of lithium amide **25** was reacted with ethyl phosphorodichloridate (3.0 mmol) in the manner described for the preparation of **23**. In this case, however, during the workup the CH_2Cl_2 solutions were stored in the cold to permit complete precipitation of the fine powdery byproduct that was removed by repeated filtration through Celite. Evaporation and crystallization (CH_2Cl_2/hexanes) afforded 0.858 g (60%) of **26** as white crystals, mp 151–172 °C (pure by ^1H NMR and TLC (ether)). Recrystallization from ether provided the analytical sample: mp 168–172 °C; IR ($CHCl_3$) 1250–1225 (P=O), 1030 (d, C–O), 940 (P–N) cm^{-1}. Anal. Calcd for $C_{30}H_{29}N_2O_2P$: C, 74.98; H, 6.08; N, 5.83. Found: C, 74.88; H, 6.10; N, 5.80.

Alkylation of 4-(*p*-Nitrobenzyl)pyridine (NBP). The reaction of alkylating agents with NBP was performed according to Dunn[30] with slight modification. Both ethanol (1.0 mL) and 0.05 M potassium hydrogen phthalate buffer (pH 4.0, 1.0 mL) were added to a sufficient number of glass screw cap test tubes so that there would be two tubes for the compound to be tested for every time period. A blank for each time period was prepared similarly except that 2.0 mL of EtOH was used. Ethanolic NBP solution (1.0 mL of 5% solution, w/v) was then added to all of the tubes. To each of the sample tubes was then added a freshly prepared 0.2 mM solution of the compound in absolute EtOH (brief warming was occasionally required to dissolve the more lipophilic compounds). The test tubes were then *tightly* capped and the solutions vortexed and placed in an 80 °C water bath. At various time intervals, a blank and two sample tubes were removed and transferred to an ice–water bath. Once ice cold the blank tube was removed, and EtOH (1.0 mL) and 0.1 N KOH solution (1.0 mL) in 80% EtOH were added. The tube was then vortexed for 20 s, and the contents were transferred to a cuvette and used to adjust a Bausch and Lomb Spectronic 20 to zero absorbance at 600 nm. Then each sample tube was removed from the bath, one at a time, and reacted with base in the same manner and the absorbance read in the same cuvette. Plots of absorbance vs time were obtained using the average of the data points of the two runs, and k' values were calculated as the slopes of the initial linear regions.

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(41) Weissberger, A.; Bach, H. *Ber.* **1931**, *64B*, 1095.