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Tributylphosphine: A Remarkable Promoting Reagent for the Ring-Opening Reaction of Aziridines

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Tributylphosphine was found to be an effective promoting reagent for ring opening of a variety of aziridines and nucleophiles to produce anti-bifunctional products in good to excellent yield. The study showed that the reaction is initiated through the attack of tributylphosphine as a nucleophile at the carbon atom of the aziridine ring.

Introduction

Phosphines are much weaker bases but stronger nucleophiles than amines, and most reactions of phosphines for synthesis depend on their nucleophilicity.[1] The range of reactions and reactivity of organophosphines is wide as they react as nucleophiles at saturated and unsaturated carbon or attack a heteroatom to give intermediates that either break down in situ to the desired products or react as synthons in their own right.[1b] Normally a stoichiometric amount of phosphine was needed in these reactions. However, considerable progress in phosphine-catalyzed reactions has been achieved in recent years.[1−3] In these reactions, organophosphines served as nucleophiles which attacked polarized double and triple bonds to initiate the reactions. There were also a few reports on the reaction of epoxides and aziridines with a stoichiometric amount of organophosphines.[4] However, no phosphine-catalyzed ring-opening reactions of aziridines with a nucleophile have ever been reported. On the other hand, ring-opening reactions of aziridines with nucleophiles provide a useful protocol in organic synthesis, and many reagents have recently been developed to realize the opening of the aziridine ring.[5] However, most of these suffered from the fact that a Lewis acid or strong base was necessary to effect the reaction.[6] Moreover, varied reaction conditions were needed for various aziridines because of the different reactivity of substrates and reagents, as well as the complexity of the structure of aziridines.[7−9] There is no general procedure suitable for various aziridines and nucleophiles. As part of a program aimed at the synthesis and applications of aziridine in organic synthesis,[10] we were interested in their ring-

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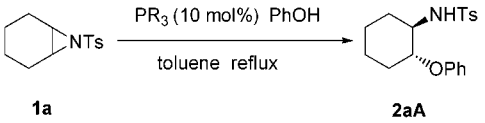
SCHEME 1



opening reactions and found that fluoride ion was an efficient promoter for the reaction of aziridines with a trimethylsilyl compound.[11] Further studies showed that many ring-opening reactions of aziridine could be efficiently carried out by using a catalytic amount of an organophosphine. Herein we disclose a novel ring-opening reaction of aziridines with a wide range of nucleophiles in the presence of a catalytic amount of organophosphine.

Results and Discussions

Ring-Opening Reactions of Aziridines in the Presence of a Phosphine. Reaction of *N*-tosylaziridine **1a** in refluxing toluene with 1.2 equiv of phenol in the presence of a catalytic amount of Bu_3P gave rise to the corresponding ring-opening product **2aA** in 95% yield (Scheme 1). The anti-stereochemistry of the product was confirmed by its ^{1}H-NOESY NMR spectrum, from which no NOE effect between two cyclic methine hydrogens was found. A control experiment showed that no reaction took place if Bu_3P was not added to the reaction system.

The structure of organophosphine strongly influences its catalytic activity. When tricyclohexylphosphine or tri(*o*-methoxyphenyl)phosphine was used as the catalyst, the yield of the product decreased to 82% and 81%, respectively. The yield decreased further to 52% if triphenylphosphine was used and no product was formed when the reaction was conducted in the presence of triethyl phosphite. The reaction rate decreased in the following order: *n*-Bu_3P > (c-$C_6H_{11})_3P$ > (*o*-MeOPh)$_3P$ > Ph_3P > $(EtO)_3P$ (unreactive). These results suggested that the catalytic activity of organophosphine was mainly governed by its nucleophilicity. Electron-donating groups on phosphorus increased the catalytic ability while electron-withdrawing groups decreased the catalytic ability. Among organophosphines tested for ring opening, Bu_3P was the most effective.

To show the usefulness of this novel organophosphine-catalyzed ring-opening reaction of aziridines, a variety of nucleophiles and various aziridines with or without an activating group on the nitrogen atom were tested (Scheme 2, Table 1).

This phosphine-catalyzed reaction of aziridines with nucleophiles provides a general and convenient way to prepare a variety of 1,2-aminoethers, diamines, and aminothioethers. It can be seen from Table 1 that, in the presence of 10 mol % of *n*-Bu_3P, various aziridines, whether the substituent on the nitrogen atom of the aziridine ring is an electron-withdrawing or a donating group, and a variety of nucleophiles including phenol, thiophenol, aliphatic mercaptan, aromatic, and aliphatic amines are suitable for this phosphine-catalyzed reaction to afford the reaction products in good to excellent yield. However, no reaction took place or only a low yield of products in the absence of tributylphosphine was obtained. The reactivity of aziridines decreased according to the decreased electron-withdrawing ability of the substituent on the nitrogen atom of aziridine. The substitution on the nucleophile had no effect on the reaction. Aromatic nucleophiles had higher reactivity than aliphatic ones. All of the reactions gave products with anti-stereochemistry, which were confirmed by the coupling constant of **2fA** (J = 9.1 Hz for two cyclic methine hydrogens at the trans-positions)[9d] and the X-ray crystallographic analysis of **2aD**. The choice of solvent is important in these reactions. Toluene is a better solvent for the reaction of aziridines with phenol while acetonitrile is a better choice for thiols and amines. For example, the reaction of aziridine **1a** and phenol in toluene gave the product in 95% yield and in acetonitrile the yield was 37%. The reaction of **1a** and nucleophile **D** provided 90% yield of product in acetonitrile; when other

SCHEME 2

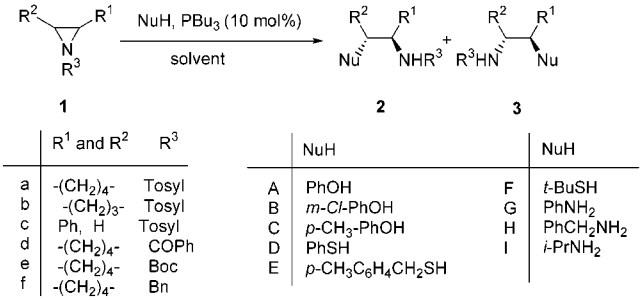


TABLE 1. The Ring-Opening Reaction of Aziridines 1 with Nucleophiles in the Presence of *n*-Bu_3P[a]

entry	substrate	NuH	product	yield, %[b]	yield, %[c]
1	**1a**	**A**	**2aA**	95	0
2	**1a**	**B**	**2aB**	97	0
3	**1a**	**C**	**2aC**	90	0
4	**1b**	**A**	**2bA**	96	0
5	**1c**	**A**	**2cA, 3cA**	86 (65:35)[d]	trace
6	**1d**	**A**	**2dA**	95	0
7	**1e**	**A**	**2eA**	57	0
8	**1f**	**A**	**2fA**	50	0
9	**1a**	**D**	**2aD**	90	15
10	**1c**	**D**	**2cD,3cD**	98 (1:1)[d]	trace
11	**1d**	**D**	**2dD**	95	trace
12	**1e**	**D**	**2eD**	75	trace
13	**1f**	**D**	**2fD**	95	30
14	**1a**	**E**	**2aE**	89	trace
15	**1a**	**F**	**2aF**	72	trace
16	**1a**	**G**	**2aG**	89	55
17	**1e**	**G**	**2eG**	70	trace
18	**1f**	**G**	**2fG**	62	trace
19	**1a**	**H**	**2aH**	85	50
20	**1a**	**I**	**2aI**	80	20

[a] Bu_3P was purified by distillation from CuI and the reactions of entries 1−8 were carried out at reflux in toluene and the reactions of entries 9−20 were carried out at room temperature in acetonitrile under Ar. [b] Isolated yields. [c] The yields from the reactions with no *n*-Bu_3P. [d] The ratio of the two regioisomers was determined by 300 MHz ^{1}H NMR.

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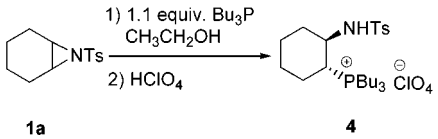
SCHEME 3



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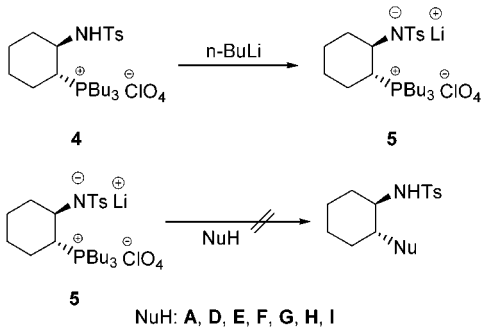

solvents were used the yield decreased (CH_2Cl_2, 65%; THF, 50%; toluene, 29%).

Studies on the Mechanism of the Ring-Opening Reaction. When 0.1 mmol of Bu_3P and 1 mmol of phenol were mixed in C_6D_6 at 25 °C, only a signal for tributylphosphine (δ −31.4 ppm) was observed in the ^{31}P NMR spectrum. Upon the addition of 1 mmol of aziridine **1a**, new signals at δ 33.7 and 34.7 ppm were observed, in addition to the original signal (δ −31.4 ppm). New signals of ^{31}P NMR at 34.4 ppm and ^{13}C NMR at 33.2 and 63.5 ppm were observed when **1a** and Bu_3P (1:1 ratio) were simply mixed and stirred for 48 h, at which point no **1a** could be detected by TLC. When tributylphosphine was replaced by triphenylphosphine, a similar new signal of ^{31}P NMR (δ 27.3 ppm) was observed. The ^{31}P chemical shifts of these new signals are in accord with those of phosphonium salts.[12] Furthermore, in contrast to the catalytic effect of phosphine, triethylamine is completely ineffective despite its stronger basicity. Only a trace of product was detected even when 200 mol % of Et_3N was used instead of Bu_3P in the reaction of **1a** with nucleophile **E**. These results revealed that the phosphine played the role of a nucleophile but not a base, and the attack of phosphine on aziridine to form a phosphonium salt is most likely the first step of the reaction.

Then the isolation of the phosphonium salt was attempted. Aziridine **1a** and tributylphosphine were mixed in CH_3CH_2OH, but the reaction failed to give an isolatable product. However, treatment of the resulting mixture with 60% $HClO_4$ gave the crystallized phosphonium salt **4** (Scheme 3). The structure of **4** was confirmed by ^1H NMR, ^{31}P NMR (δ 35.5 ppm), elemental analysis, and X-ray diffraction analysis. Deprotonation of phosphonium **4** with *n*-BuLi provided the phosphonium salt **5**. We then subjected **5** to each nucleophile to see whether the phosphonium salt would undergo nucleophilic displacement; no displacement product was observed (Scheme 4). However, in the presence of 10 mol % of **5**, the ring opening of **1a** with nucleophile (**A**, **D**, **E**, and **F**) proceeded smoothly and gave rise to the corresponding ring-opening

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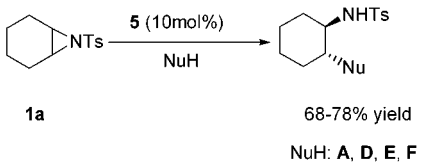
SCHEME 5



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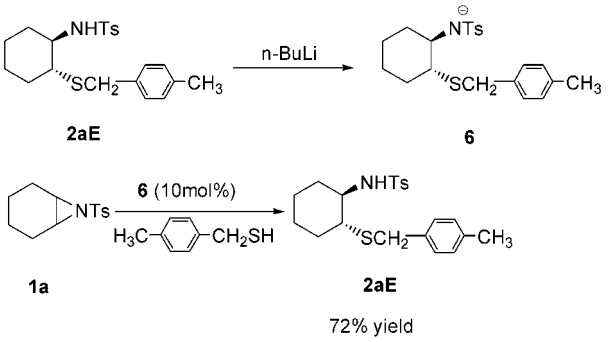

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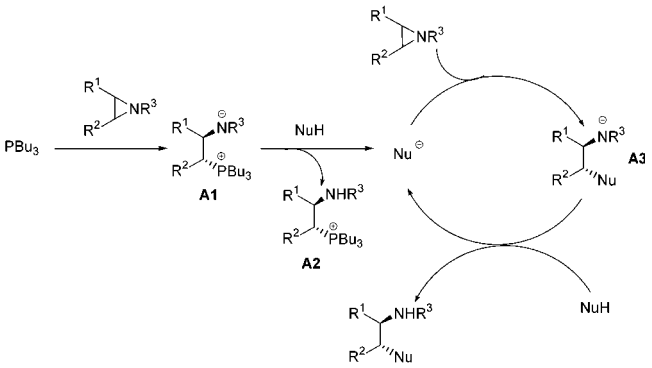

products in 68−78% yield (Scheme 5). In addition, not only **5** can catalyze this reaction; **6**, the deprotonated product of **2aE**, can also catalyze the reaction of **1a** with **E** (Scheme 6).

According to these experimental facts, a possible mechanism can be proposed (Scheme 7). Tributylphosphine attacks the aziridine to form a phosphonium intermediate **A1**, which could deprotonate NuH to form intermediate **A2** and Nu^-. Then Nu^- reacts with aziridine to give the ring-opened intermediate **A3**, which reacts with another NuH to provide the product and regenerate the Nu^- to complete the catalytic cycle. The organophosphine acts as a nucleophilic trigger to produce **A1**, which serves as a base to deprotonate the nucleophile.

It was noted that the quantity of phosphine used still has a significant influence on the yield and the rate of the reaction. For example, with 100 mol % of Bu_3P, the reaction of **1a** with **E** was completed in only 1 h in 98% yield, while 48 h was needed to give a 89% yield with 10 mol % of phosphine and 56% yield with 5 mol % of phosphine. Also, compared with the corresponding control experiments, the yield did not change when the reaction of **1a** with nucleophiles **G**, **H**, and **I** was conducted in the presence of **5**. In the ring opening of aziridine with amine and thiophenol in some cases, the phosphine might not be necessary but can promote the reaction. The role of phosphine in these reactions is still not clear.

On the basis of these findings, a novel and efficient nonmetallic catalyzed ring-opening reaction of various aziridines with a wide range of nucleophiles under mild conditions was developed, which opens the way to a variety of 1,2-bifunctional products.[13] The further investigations of the mechanism in detail and the scope of these reactions are in progress.

Experimental Section

General Experimental Conditions. All reactions were performed under an atmosphere of either dry argon or nitrogen with oven-dried glassware. Solvents were distilled under an atmosphere of nitrogen before use. THF and toluene were distilled from sodium benzophenone ketal. Dichloromethane and acetonitrile were distilled from calcium hydride. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ and the chemical shifts were referenced to $CHCl_3$ (δ 7.27 ppm). The chemical shifts of ^{31}P NMR were referenced to external 85% H_3PO_4. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. IR spectra were measured in cm^{-1}.

General Procedure of the Ring-Opening Reaction of Aziridines 1 with Nucleophiles A−I Catalyzed by Bu_3P. To a stirred solution of aziridine **1** (0.5 mmol) and nucleophiles **A**−**I** (0.55 mmol) in the corresponding solvent (2.0 mL) was added tributylphosphine (0.013 mL, 0.05 mmol) under argon, and the resulting mixture was stirred at room temperature (CH_3CN) or at reflux (toluene) until complete consumption of the substrate (monitored by TLC). The solvent was removed in a vacuum and the crude product was purified by flash column chromatography to provide the corresponding product.

***N*-(2-Phenoxyl)cyclohexyl-4-methylbenzensulfonamide (2aA).** White solid; mp 146−148 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.25−1.33 (m, 4H), 1.56−1.75 (m, 2H), 2.02−2.05 (m, 1H), 2.21−2.24 (m, 1H), 2.43 (s, 3H), 3.27−3.40 (m, 1H), 4.11−4.25 (m, 1H), 4.76 (d, J = 3.6 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 6.94 (t, J = 7.5 Hz, 1H,), 7.21−7.30 (m, 4H), 7.76 ppm (d, J = 8.2 Hz, 2H); IR (film) $\tilde{\nu}$ 3297 cm^{-1} (NH), 1601 cm^{-1} (Ph); EI-MS m/z (%) 346 (37) [M^+ + H], 252 (100) [M^+ − PhOH]. Anal. Calcd for $C_{19}H_{23}NSO_3$: C, 66.06; H, 6.71; N, 4.05. Found: C, 65.91; H, 6.81; N, 3.81.

***N*-[2-(3-Chlorophenoxy)cyclohexyl]-4-methylbenzenesulfonamide (2aB).** White solid; mp 122−124 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.26−1.36 (m, 4H), 1,63−1.71 (m, 2H), 2.01−2.20 (m, 2H), 2.42 (s, 3H), 3.27−3.30 (m, 1H), 3.95−4.00 (m, 1H), 4.89 (d, J = 5.9 Hz, 1H), 6.58−6.60 (m, 2H), 6.87−6.90 (m, 1H), 7.09−7.15 (m, 1H), 7.26 (t, J = 4.2 Hz, 2H), 7.74 ppm (d, J = 8.3 Hz, 2H); IR (neat) 3304, 1594, 1382 cm^{-1}; EI-MS m/z (%) 379 (M^+, 5), 252 (100), 172 (21). Anal. Calcd for $C_{19}H_{22}ClNSO_3$: C, 60.07; H, 5.84; N, 3.69. Found: C, 60.35; H, 5.99; N, 3.67. Anal. Calcd for $C_{19}H_{23}N_2SO_5$: C, 58.45; H, 5.68; N, 7.17. Found: C, 58.37; H, 5.49; N, 6.94.

***N*-[2-(4-Methylphenoxy)cyclohexyl]-4-methylbenzenesulfonamide (2aC).** White solid; mp 127−128 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.26−1.34 (m, 4H), 1.57−1.70 (m, 2H), 2.02−2.05 (m, 1H), 2.17−2.24 (m, 1H), 2.27 (s, 3H), 2.42 (s, 3H), 3.20−3.23 (m, 1H), 3.94−3.97 (m, 1H), 4.88 (d, J = 4.6 Hz, 1H), 6.62 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.76 ppm (d, J = 8.2 Hz, 2H); IR (neat) 3323, 1615, 1383 cm^{-1}; EI-MS m/z (%) 359 (M^+, 10), 252 (100), 155 (46). Anal. Calcd for $C_{20}H_{25}NSO_3$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.85; H, 7.08; N, 3.88.

***N*-(2-Phenoxy)cyclopentyl-4-methylbenzenesulfonamide (2bA).** White solid; mp 115−117 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.40−1.47 (m, 1H), 1.71−1.81 (m, 3H), 1.98−2.09 (m, 2H), 2.38 (s, 3H), 3.66−3.72 (m, 1H), 4.49−4.52 (m, 1H), 4.91 (d, J = 6.5 Hz, 1H), 6.76 (d, J = 7.8 Hz, 2H), 6.89−6.94 (m, 1H), 7.19−7.26 (m, 4H), 7.75 ppm (d, J = 8.0 Hz, 2H); IR (neat) 3289, 1600, 1382 cm^{-1}; EI-MS m/z (%) 331 (M^+, 6), 238 (100), 172 (54). Anal. Calcd for $C_{18}H_{21}NSO_3$: C, 65.23, H; 6.39; N, 4.23. Found: C, 65.11; H, 6.50; N, 4.00.

1-Phenoxymethyl-*S*-4-methylphenyl-benzenemethansulfonamide (2cA) and 2-Phenoxy-*S*-4-methylphenyl-benzeneethansulfonamide (3cA). Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.35 (s, 3H), 2.39 (s, 3H), 3.25 (dd, J = 13.6, 8.9 Hz, 1H), 3.42 (dd, J = 13.5, 3.8 Hz, 1H), 4.02 (m, 2H), 4.68 (t, J = 5.3 Hz, 1H), 5.11 (dd, J = 8.9, 3.8 Hz, 2H), 5.44 (br, 1H), 6.73 (t, J = 8.3 Hz, 3H), 6.85−6.96 (m, 3H), 7.11−7.17 (m, 3H), 7.20−7.32 (m, 15H), 7.61 (d, J = 8.3 Hz, 2H), 7.72 ppm (d, J = 8.3 Hz, 2H); IR (film) $\tilde{\nu}$ 3280 (NH), 1599 cm^{-1} (Ph); EI-MS m/z (%) 367 (1) [M^+], 274 (93) [M^+ − PhOH]; HRMS calculated for $C_{21}H_{21}NSO_3$ 367.1234, found 367.1240. Anal. Calcd for $C_{21}H_{21}NSO_3$: C, 68.64, H, 5.76; N, 3.81. Found: C, 68.63; H, 5.94; N, 3.72.

***N*-[2-(Phenoxy)cyclohexyl]benzamide (2dA).** White solid; mp 162−164 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.38−1.61 (m, 5H), 1.82−1.85 (m, 1H), 2.15−2.17 (m, 1H), 2.27−2.32 (m, 1H), 4.17−4.30 (m, 2H), 6.11 (d, J = 5.5 Hz, 1H), 6.93−6.99 (m, 3H), 7.23−7.28 (m, 2H), 7.35−7.45 (m, 3H), 7.60−7.63 ppm (m, 2H); IR (neat) 3305, 1639, 1601 cm^{-1}; EI-MS m/z (%) 296 (MH^+, 2), 202 (30), 105 (100). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17, N, 4.74. Found: C, 77.36; H, 7.15; N, 4.58.

***N*-Boc-2-(phenoxy)cyclohexylamine (2eA).** White solid; mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.25−1.63 (m, 15H), 2.13−2.15 (m, 2H), 3.65−3.72 (m, 1H), 4.04 (dt, J = 9.1, 3.8 Hz, 1H), 4.53 (d, J = 6.3 Hz, 1H), 6.90−6.95 (m, 3H), 7.23−7.29 ppm (m, 2H); IR (film) $\tilde{\nu}$ 3329 (NH), 1689 (C═O), 1391 cm^{-1} (CH_3); EI-MS m/z (%) 291 (4) [M^+], 174 (32), 142 (100); HRMS calculated for $C_{17}H_{25}NO_3$ 291.1850, found 291.1862. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07, H; 8.65; N, 4.81. Found: C, 70.15; H, 8.39; N, 4.59.

***N*-(2-(Phenoxy)cyclohexyl)benzenemethanamine (2fA).** Yellow solid; mp 42−44 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.23−1.36 (m, 4H), 1.73−1.75 (m, 2H), 2.11−2.15 (m, 3H), 2.79 (dt, J = 9.1, 4.4 Hz, 1H), 3.84 (ABq, J = 13.1 Hz, 2H), 4.09 (dt, J = 9.0, 4.3 Hz, 1H), 6.91−6.95 (m, 3H), 7.23−7.31 ppm (m, 7H); IR (film) $\tilde{\nu}$ 3330 (NH), 1600 cm^{-1} (CH_3); EI-MS m/z (%) 281 (17), [M^+], 188 (53) [M^+ − PhOH], 91 (100); HRMS calculated for $C_{19}H_{23}NO$ 281.1867, found 281.1852. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10, H; 8.24; N, 4.98. Found: C, 81.01; H, 8.02; N, 4.88.

***N*-(2-Phenylthiocyclohexyl)-4-methylbenzenesulfonamide (2aD).** White solid; mp 130−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.20−1.50 (m, 4H), 1.50−1.75 (m, 2H), 2.00−2.10 (m, 1H), 2.20−2.30 (m, 1H), 2.45 (s, 3H), 2.80−3.00 (m, 2H), 5.10−5.20 (d, J = 3.6 Hz, 1H), 7.20−7.40 (m, 7H), 7.75 ppm (d, J = 8.3 Hz, 2H); IR (film) $\tilde{\nu}$ 3265 cm^{-1} (NH); EI-MS m/z (%) 361 (7) [M^+], 252 (13) [M^+ − PhS]. Anal. Calcd for $C_{19}H_{23}NO_2S_2$: C, 63.13; H, 6.41; N, 3.87. Found: C, 63.07; H, 6.48; N, 3.91.

1-(Phenylthio)methyl-*S*-(4-methylphenyl)benzenemethansulfonylamide and 2-Phenylthio-*S*-(4-methylphenyl)benzeneethansulfonylamide (2cD and 3cD). Colorless liquid; ^{1}H NMR ($CDCl_3$/TMS) δ 2.35 (s, 3H), 2.42 (s, 3H), 3.18−3.22 (m, 2H), 3.34−3.39 (m, 2H), 4.13 (t, J = 7.2 Hz, 1H), 4.30 (q, J = 6.7 Hz, 1H), 4.74 (br, 1H), 5.33 (br, 1H), 7.08−7.27 (m, 24H), 7.50 (d, J = 8.2 Hz, 2H), 7.64 ppm (d, J = 8.2 Hz, 2H); IR (neat) 3290, 3059, 1599 cm^{-1}; EI-MS m/z (%) 383 (M^+, 1.67), 260 (100), 199 (78). Anal. Calcd for $C_{21}H_{21}NO_2S_2$: C, 65.76; H, 5.52; N, 3.65. Found: C, 65.66; H, 5.75; N, 3.58.

***N*-[2-(Phenylthio)cyclohexyl]benzamide (2dD).** White solid; mp 126−128 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.10−1.50 (m, 4H), 1.60−1.75 (m, 2H), 2.05−2.20 (m, 1H), 2.25−2.40 (m, 1H), 2.90−3.10 (m, 1H), 3.75−3.90 (m, 1H), 6.20 (d, J = 6.6 Hz, 1H), 7.10−7.50 (m, 8H), 7.60 ppm (d, J = 8.6 Hz, 2H); IR (film) 3302, 2933, 1637 cm^{-1}; EI-MS m/z (%) 311 (M^+, 1), 273 (6), 210 (27), 190 (100). Anal. Calcd for $C_{19}H_{21}NOS$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.16; H, 6.87; N, 4.33.

(13) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

***N*-Boc-2-(phenylthio)cyclohexylamine (2eD).**[8e] White solid; mp 108−110 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 1.10−1.30 (m, 3H), 1.40 (s, 9H), 1.50−1.75 (m, 3H), 1.95−2.05 (m, 1H), 2.05−2.20 (m, 1H), 2.85 (dt, J = 10.3, 3.7 Hz, 1H), 3.30−3.40 (m, 1H), 4.62 (d, J = 7.3 Hz, 1H), 7.10−7.30 (m, 3H), 7.30−7.50 ppm (m, 2H); IR (film) 3346, 2932, 1686, 1532 cm^{-1}; EI-MS *m*/*z* (%) 307 (M^+, 2.4), 252 (2), 190 (23), 57 (100); HRMS calculated for $C_{17}H_{25}NO_2S$ 307.1564, found 307.1585.

***N*-(2-(Phenylthio)cyclohexyl)benzenemethanamine (2fD).** Yellow liquid; ^{1}H NMR ($CDCl_3$/TMS) δ 1.25−1.42 (m, 4H), 1.69−1.72 (m, 2H), 2.02−2.21 (m, 2H), 2.43−2.46 (m, 1H), 2.92−3.00 (m, 2H), 3.71−3.98 (m, 2H), 7.23−7.51 ppm (m, 10H); IR (neat) 3280, 3061, 1583 cm^{-1}; EI-MS *m*/*z* (%) 297 (M^+, 2), 91 (100), 106 (79), 188 (24). HRMS calculated for $C_{19}H_{23}NS$ 297.1551, found 297.1507. Anal. Calcd for $C_{19}H_{23}NS$:: C, 76.72, H; 7.79; N, 4.71. Found: C, 76.45; H, 8.04; N, 4.46.

***N*-2-[(4-Methylphenyl)methylthio]cyclohexyl-4-methylbenzenesulfonamide (2aE).** White solid; mp 100−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.01−1.50 (m, 4H), 1.52−1.73 (m, 2H), 1.92−2.12 (m, 1H), 2.14−2.27 (m, 1H), 2.27 (s, 3H), 2.33−2.38 (m, 1H), 2.41 (s, 3H), 2.78−2.92 (m, 1H), 3.45−3.57 (m, 2H), 5.03 (d, J = 2.4 Hz, 1H), 7.10−7.30 (m, 6H), 7.74−7.77 ppm (d, J = 8.2 Hz, 2H); IR (film) $\tilde{\nu}$ 3309 (NH), 1597 (Ph), 1383 cm^{-1} (CH_3); EI-MS *m*/*z* (%) 389 (1) [M^+], 234 (100); HRMS calculated for $C_{21}H_{27}NS_2O_2$ 389.1449, found 389.1456. Anal. Calcd for $C_{21}H_{27}NS_2O_2$: C, 64.74, H; 6.99; N, 3.60. Found: C, 64.56; H, 6.90; N, 3.63.

***N*-[2-(1,1-Dimethyl)ethylthio]cyclohexyl-4-methylbenzenesulfonamide (2aF).** Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.29 (s, 9H), 1.45−1.67 (m, 6H), 2.04−2.17 (m, 2H), 2.42 (s, 3H), 2.43−2.58 (m, 1H), 2.59−2.81 (m, 1H), 5.37 (br, 1H), 7.30 (d, ^3J = 7.9 Hz, 2H), 7.76 ppm (d, ^3J = 8.0 Hz, 2H); IR (film) $\tilde{\nu}$ 3275 (NH), 1598 (Ph), 1393 cm^{-1}(CH_3); EI-MS *m*/*z* (%) 341 (44) [M^+], 286 (10) [$M^+ - C_4H_9$], 252 (11) [$M^+ - C_4H_9SH$]; HRMS calculated for $C_{17}H_{27}NS_2O_2$ 341.1407, found 341.1510. Anal. Calcd for $C_{17}H_{27}NS_2O_2$: C, 59.78, H; 7.97; N, 4.10. Found: C, 60.05; H, 7.80; N, 3.98.

***N*-(2-Phenylamino)cyclohexyl-4-methylbenzenesulfonylnamide (2aG).**[9b] White solid; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.01−1.45 (m, 4H), 1.50−1.67 (m, 2H), 1.95−2.20 (m, 2H), 2.40 (s, 3H), 2.85−3.05 (m, 3H), 5.08 (br, 1H), 6.45 (d, J = 7.4 Hz, 2H), 6.38−6.5 (m, 1H), 7.05−7.30 (m, 4H), 7.81 ppm (d, J = 7.3 Hz, 2H); EI-MS *m*/*z* (%) 344 (20) [M^+], 96 (100).

***N*-Phenyl-*N*′-Boc-1,2-cyclohexanediamine (2eG).**[9b] White solid; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.08−1.48 (m, 12H), 1.52−1.75 (m, 3H), 1.92−2.08 (m, 1H), 2.12−2.24 (m, 1H), 2.85−3.05 (m, 1H), 2.31−2.50 (m, 1H), 4.33 (s, 1H), 4.46 (d, J = 7.8 Hz, 1H), 6.51 (d, J = 7.7 Hz, 2H), 6.60 (t, J = 7.3 Hz, 1H), 7.07−7.13 ppm (m, 2H); EI-MS *m*/*z* (%) 290 (77) [M^+], 132 (100).

***N*-Phenyl-*N*′-benzyl-1,2-cyclohexanediamine (2fG).**[9d] White solid; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.1 (m, 1H), 1.23−1.40 (m, 4H), 1.68−1.80 (m, 2H), 2.08−2.24 (m, 2H), 2.34 (td, J = 9.6, 3.9 Hz, 1H), 2.46−2.86 (br, 1H), 3.17 (td, J = 9.8, 3.9 Hz, 1H), 3.80 (ABq, J = 13.3 Hz, 2H), 6.57−6.66 (m, 3H), 7.06−7.16 ppm (m, 7H); EI-MS *m*/*z* (%) 280 (57) [M^+], 91 (100).

***N*-(2-Phenylmethylamino)cyclohexyl-4-methylbenzenesulfonylnamide (2aH).**[9b] White solid; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.06−1.41 (m, 6H), 1.56−1.63 (m, 2H), 1.77−1.82 (m, 1H), 2.29−2.34 (m, 1H), 2.38 (s, 3H, CH_3), 2.84−2.92 (m, 1H), 3.64 (ABq, J = 13.2 Hz, 2H), 7.21−7.36 (m, 7H), 7,74 ppm (d, J = 8.2 Hz, 2H); EI-MS *m*/*z* (%) 359 (87) [M + H^+], 91 (100).

***N*-[2-(1-Methylethylamino)]cyclohexyl-4-methylbenzenesulfonylnamide (2aI).** White solid; mp 112−114 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 0.94 (dd, J = 6.1, 2.4 Hz, 6H, $CH(CH_3)_2$), 1.11−1.26 (m, 4H), 1.61−1.67 (m, 2H), 2.05−2.09 (m, 1H), 2.16−2.23 (m, 2H), 2.42 (s, 3H), 2.45−2.47 (m, 1H), 2.86 (m, 1H), 5.68 (br, 1H), 7.30 (d, ^3J = 8.1 Hz, 2H), 7.76 ppm (d, J = 8.2 Hz, 2H); IR (film) $\tilde{\nu}$ 3244 (NH), 1597 cm^{-1} (Ph); EI-MS *m*/*z* (%) 311 (28) [M + H^+], 155 (100). Anal. Calcd for $C_{16}H_{26}NO_2S$: C, 61.90, H, 8.44, N, 9.02. Found: C, 61.77, H, 8.38, N, 8.78.

Mechanistic Study. (1) The Reaction of 1a with E in the Presence of 1 equiv of Bu_3P: To a stirred solution of aziridine **1a** (126 mg, 0.5 mmol) and **E** (0.3 mL, 0.6 mmol) in CH_3CN (2.0 mL) was added tributylphosphine (0.13 mL, 0.5 mmol) under argon and the resulting mixture was stirred at room temperature. After 1 h the substrate disappeared (monitored by TLC). The solvent was removed in a vacuum and the crude product was purified by flash column chromatography to provide **2aE** in 99% yield.

(2) The Reaction of 1a with E in the presEnce of 1.2 equiv of *n*-BuLi. To a stirred solution of aziridine **1a** (126 mg, 0.5 mmol) and **E** (0.3 mL, 0.6 mmol) in toluene (2.0 mL) was added *n*-BuLi (0.4 mL, 1.6M in hexane, 0.65 mmol) at −78 °C under argon, and the resulting mixture was stirred at room temperature until **1a** disappeared (by TLC). The solvent was removed in a vacuum and the crude product was purified by flash column chromatography to provide **2aE** in 78% yield.

(3) The Reaction of 1a with E in the Presence of a Catalytic Amount of 2aE and BuLi. To a stirred solution of **2aE** (19 mg, 0.05 mmol) in toluene (2.0 mL) was added *n*-BuLi (0.031 mL, 1.6 M in hexane, 0.05 mmol) at −78 °C under argon and the resulting mixture was stirred at room temperature for 1 h. Then **1a** (126 mg, 0.5 mmol) and **E** (0.3 mL, 0.6 mmol) were added, and the mixture was stirred until **1a** disappeared (determined by TLC). The solvent was removed in a vacuum and the crude product was purified by flash column chromatography to provide **2aE** in 72% yield.

The structure of product **2aE** obtained in the study was confirmed to be identical with that obtained by the General procedure by ^{1}H NMR, ^{1}H NOESY, melting point, and HPLC.

(4) The Preparation of Phosphonium Salt 4. To a suspension of Bu_3P (0.28 mL, 1.1 mmol) in ethanol (10 mL) was added **1a** (252 mg, 1 mmol) to give a clear solution after a few minutes. The mixture was then stirred for 36 h at room temperature after which addition of 60% aqueous perchloric acid (3 mL) and cooling at 0 °C gave solid product. After recrystallization from CH_2Cl_2, a good crystal could be obtained in 46% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 0.99−1.03 (m, 11H), 1.10−1.37 (m, 3H), 1.55−1.63 (m, 13H), 1.74−1.77 (m, 1H), 1.91−1.93 (m, 1H), 2.30−2.40 (m, 6H), 2.42 (s, 3H), 2.93−2.98 (m, 1H), 3.41−3.46 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.78 ppm (d, J = 8.2 Hz, 2H); ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C, 85% H_3PO_4) δ 35.46; EI-MS *m*/*z* (%) 283 (100), 253 (6). Anal. Calcd for $C_{25}H_{45}NO_6PS$: C, 54.19; H, 8.19; N, 2.53. Found: C, 54.13; H, 7.93; N, 2.38.

(5) Reaction of Phosphonium 4 with Nucleophile. To a stirred solution of **4** (56 mg, 0.1 mmol) in THF (2.0 mL) was added *n*-BuLi (0.031 mL, 1.6 M in hexane, 0.05 mmol) at −78 °C under argon; the resulting mixture was stirred at room temperature for 1 h, the NuH (**A**, **D**, **E**, **F**, **G**, **H**, **I**, 0.5 mmol) was added, and the mixture was stirred for 48 h. No reaction took place (TLC detection).

(6) Reaction of 1a with Nucleophile in the Presence of Phosphonium 4. To a stirred solution of **4** (28 mg, 0.05 mmol) in THF (2.0 mL) was added *n*-BuLi (0.031 mL, 1.6 M in hexane, 0.05 mmol) at −78 °C under argon and the resulting mixture was stirred at room temperature for 1 h, then **1a** (126 mg, 0.5 mmol) and NuH (**A**, **D**, **E**, **F**, **G**, **H**, **I**, 0.5 mmol) were added, and the mixture was stirred for 48 h. The solvent was removed in a vacuum and the crude product was purified by flash column chromatography to provide the corresponding product.

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Supporting Information Available: ORTEP drawing of compounds **2aD** and **4** as well as their X-ray crystallographic files. This material is available free of charge via the Internet at http://pubs.acs.org.

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