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Efficient Ring-Opening Reaction of Epoxides and Aziridines Promoted by Tributylphosphine in Water

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Tributylphosphine was found to be an effective promoting reagent for the ring-opening reaction of various epoxides and aziridines with nucleophile to produce corresponding anti-bifunctional products in moderate to excellent yields in water.

Introduction

Ever since Breslow studied Diels−Alder reactions in aqueous media,[1] many organic reactions that are traditionally carried out exclusively in organic solvents have also been successfully performed in aqueous media. Potential advantages of using water as a solvent are its low cost, safety, and ease of use. Water is also environmentally benign. Novel reactions in which the use of water as a solvent is critical have also been sporadically reported in the literature over the past few decades.[2] On the other hand, epoxides and aziridines have recently attracted increasing attention as versatile intermediates in organic synthesis.[3,4] Considerable progress has been achieved in the nucleophilic ring-opening reactions of aziridines and epoxides. However, most of these reactions have suffered from the fact that they require a strong base or Lewis acid. Moreover, there is no general procedure suitable for various aziridines, epoxides and nucleophiles because of their different reactivities. Finally, most of these reactions need to be carried out in organic solvents. Therefore, a new methodology for the ring-opening of epoxides and aziridines under more convenient and general conditions is needed.[5] In the course of our studies on the synthesis of aziridines and epoxides and their applications in organic synthesis,[6] we developed a novel phosphine-mediated ring-opening reaction of various aziridines with a wide range of nucleophiles.[7] Further studies showed that this phosphine-mediated ring-opening reaction is suitable not only for aziridines but also for epoxides, and most importantly that the reaction can proceed in water. We describe here efficient and practical procedures for the ring-opening reactions of epoxides and aziridines with various nucleophiles in water in the presence of a catalytic amount of organophosphine.[5b,8]

Results and Discussions

Wittig reported that an epoxide could be deoxygenated by phosphines, which occurs via the attack of a carbon atom of epoxides by phosphine followed by an elimination reaction.[9] However, we found that in the presence of *p*-$CH_3C_6H_4CH_2SH$ as a nucleophile, the course of the deoxygenation reaction was entirely altered from the production of styrene oxide and tributylphosphine. Instead, a ring-opened addition product was obtained in high yield (Scheme 1). A control experiment showed that no reaction took place in the absence of Bu_3P.

On the other hand, when cyclohexene oxide was used as the substrate, no reaction took place under the same

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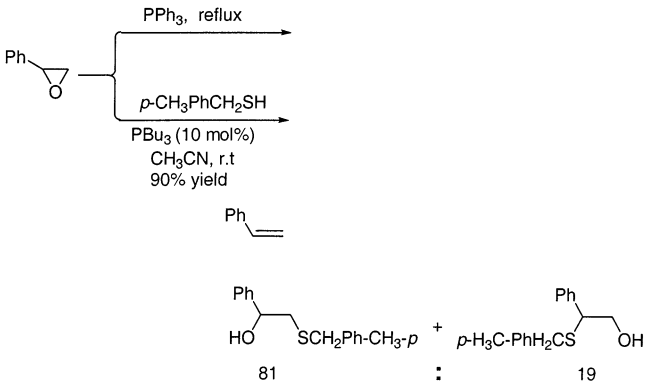
SCHEME 1



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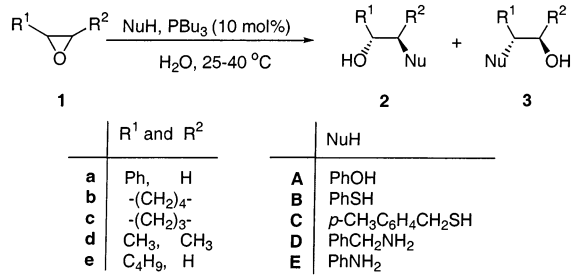


conditions. However, the reaction proceeded smoothly with water as a solvent. To demonstrate the usefulness of this novel aqueous organophosphine-mediated ring-opening reaction of epoxides, a variety of nucleophiles and epoxides were tested (Scheme 2, Table 1).

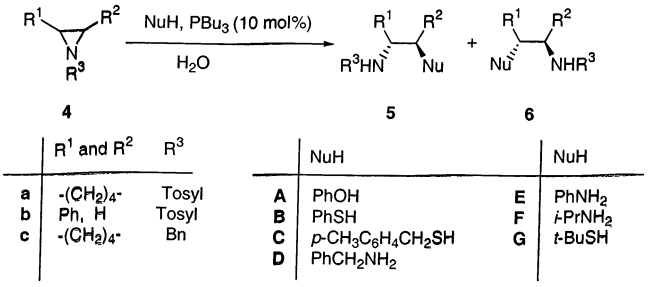
As shown in Table 1, various epoxides and nucleophiles, including phenol, thiophenol, aliphatic mercaptan, and aromatic and aliphatic amines, are suitable for this aqueous phosphine-catalyzed reaction to give the corresponding ring-opened products in moderate to good yield, while no reaction took place or the product was obtained only in low yield in the absence of tributylphosphine. The anti-stereochemistry of all of the products was confirmed from their coupling constants**.** Another notable feature of this method is that many reactions which did not take place in organic solvent proceeded smoothly in aqueous media (entries 1 and 4−11 in Table 1). In the literature, various reaction conditions have been used for ring-opening reactions of epoxides with different nucleophiles.[10,11] Reaction conditions suitable for aromatic

TABLE 1. Ring-Opening Reaction of Epoxides 1 with Nucleophiles in Water and in the Presence of *n*-Bu_3P[a]

entry	substrate	NuH	product	yield [%][b] (**2**:**3**)	yield [%][c] (**2**:**3**)	yield [%][d] (**2**:**3**)
1	**1a**	**A**	**2aA**, **3aA**	61 (90:10)[e]	0	trace
2	**1a**	**B**	**2aB**, **3aB**	88 (67:33)[e]	41 (20:80)[e]	96 (85:15)[e]
3	**1a**	**C**	**2aC**, **3a**C	88 (67:33)[e]	trace	90 (81:19)[e]
4	**1b**	**B**	**2bB**	72	15	0
5	**1b**	**D**	**2bD**	78	39	trace
6	**1b**	**E**	**2bE**	64	25	trace
7	**1c**	**B**	**2cB**	78	16	trace
8	**1c**	**E**	**2cE**	72	26	trace
9	**1d**	**B**	**2dB**	83	34	trace
10	**1d**	**E**	**2dE**	78	34	trace
11	**1e**	**B**	**2eB**	85 (>95:5)	trace	trace

[a] Bu_3P was purified by distillation from CuI and the reactions were carried out at room temperature under Ar. [b] Isolated yields. [c] Isolated yields in the absence of *n*-Bu_3P. [d] Isolated yields from the reactions run in CH_3CN in the presence of Bu_3P. [e] Ratios of the two regioisomers were determined by 300-MHz ^1H NMR.

SCHEME 3



nucleophiles have not always been suitable for aliphatic nucleophiles. For example, several reported reactions of epoxides with aromatic amines could not be applied to benzylamine.[10a,11] Ring-opening reactions of epoxides with benzylamine have been reported to occur only in the presence of $Yb(OTf)_3$[12] or 100 mol % of $LiClO_4$[13] in organic solvent. In our case, the corresponding product **2bD** was obtained in 78% yield in water at room temperature in the presence of tributylphosphine (entry 5, Table 1), while the reaction of aromatic amine also gave product **2bE** in good yield (entry 6, Table 1). The reaction can be easily scaled up to 100 mmol, and many products can be easily isolated by simple filtration and washing with petroleum ether. Interestingly, the presence of Bu_3P affects not only the yield but also the regioselectivity of the reactions of **1a** (entry 2). In the presence of Bu_3P, the normal mode of epoxide opening was observed, and the product **2**, for which the nucleophile attacked the least-hindered carbon atom, is favored. On the other hand, in the absence of Bu_3P, the regiochemistry of the epoxide was reversed.

Further studies showed that this aqueous ring-opening reaction can also be extended to aziridines, and water is also a good solvent for the ring-opening of aziridines in the presence of a catalytic amount of tributylphosphine (Scheme 3, Table 2).

As shown in Table 2, various aziridines, regardless of whether the substituent at the nitrogen atom of the aziridine ring is an electron-withdrawing or an electron-

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TABLE 2. The Ring-Opening Reaction of Aziridines 4 in Water Catalyzed by *n*-Bu_3P[a]

entry	substrate	NuH	product	yield [%][b]	yield %][c]	yield [%][d]
1	**4a**	**A**	**5aA**	85[e]	0	0
2	**4a**	**B**	**5aB**	98	25	90
3	**4a**	**C**	**5aC**	99	trace	89
4	**4a**	**G**	**5aG**	88	trace	72
5	**4a**	**D**	**5aD**	99	65	85
6	**4a**	**E**	**5aE**	98	50	89
7	**4a**	**F**	**5aF**	61	trace	80
8	**4b**	**B**	**5bB**, **6bB**	98 (50/50)[f]	trace	98 (50:50)[f]
9	**4c**	**B**	**5cB**	62	trace	95
10	**4c**	**E**	**5cE**	91	27	62

[a] Bu_3P was purified by distillation from CuI and the *reactions* were carried out at room temperature under Ar. [b] Isolated yields. [c] Isolated yields in the absence of *n*-Bu_3P. [d] Isolated yields in CH_3CN in the presence of Bu_3P. [e] 0.2 mL of CH_3CN was added to the reaction. [f] The ratios of the two regioisomers was determined by 300-MHz ^1H NMR.

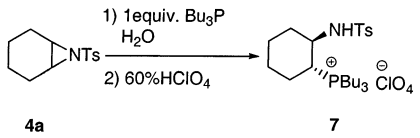
donating group, and various nucleophiles, including phenol, thiophenol, aliphatic mercaptan, and aromatic and aliphatic amines, are suitable for this phosphine-catalyzed reaction. The corresponding ring-opening reaction products were obtained in good to excellent yield, while no reaction took place or the products were obtained in only low yield in the absence of tributylphosphine. Reactions carried out in water were faster than those in organic solvent. For example, to achieve the same yields, the reaction of **4a** with nucleophiles **B**−**G** needed 36−56 h in organic solvent, but only 12 h in water. Also, the reaction of aziridine **1a** with phenol failed to give the desired product in organic solvent in the presence of 10 mol % of tributylphosphine, unless it was warmed from room temperature to reflux. However, this reaction occurred at room temperature with the addition of 20% (v/v) water to the mixture. Under optimal conditions, a 1:10 mixture of CH_3CN and water was the best solvent, while no reaction occurred in water alone. Again, the anti-stereochemistry of the products was established by NMR spectroscopy.

The structure of an organophosphine strongly influences its catalytic activity. The reaction of aziridine **1a** with nucleophile **C** was more sluggish when tricyclohexylphosphine or triphenylphosphine was used as a catalyst instead of tributylphosphine, and no product was obtained in the presence of triethyl phosphite.

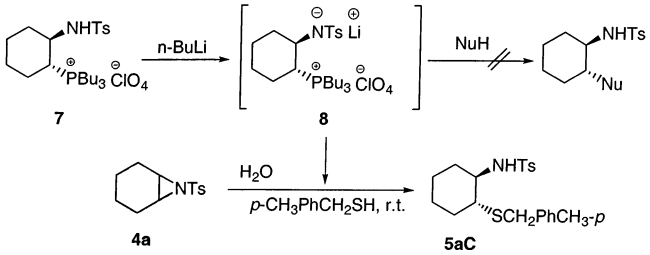
We have shown that in the tributylphosphine-promoted ring-opening reaction of aziridines with nucleophiles, the tributylphosphine acts as a nucleophilic trigger to attack the carbon atom of the aziridine ring, and thus initiates the reaction.[7] To show the role of phosphine in aqueous solution, PhSH and Bu_3P were mixed in a 2:1 ratio in a 1:1 mixed solvent of D_2O and THF. Except for the signal of Bu_3P, no new signal of ^{31}P NMR was observed. However, for the mixture of epoxide **1e** and Bu_3P in a 1:1 ratio in a 1:2 mixed solvent of D_2O and THF, new signals at δ 37.2 and 37.3 ppm were observed, in addition to the original signal (δ −28.2 ppm).

Treatment of the reaction mixture of aziridine **4a** and Bu_3P with 60% $HClO_4$ gave phosphonium salt **7**, which was confirmed to be identical with that prepared in organic solvent[7] (Scheme 4). Deprotonation of phosphonium **7** with n-BuLi provided phosphonium salt **8**, which failed to give a displacement product when reacted with

SCHEME 4



SCHEME 5



nucleophile **A**, **B**, or **C**. However, product **5aC** was isolated in 48% yield when the aziridine **4a** reacted with nucleophile **C** in water in the presence of deprotonated phosphonium salt **8** (Scheme 5). In addition, in the presence of 10 mol % of deprotonated product **5aC**, the reaction of **4a** with **C** also took place under the same conditions. These observations are similar to those in organic solvent.[7]

On the basis of these results, phosphine plays the same role in aqueous solution as it does in organic solvent. Phosphine attacks the ring of epoxide or aziridine to form the salt, which acts as a base to generate the anion of the nucleophile. The Nu^- reacts with aziridine or epoxide to give the ring-opened intermediate, which reacts with another nucleophile to provide the product and regenerate the Nu^- to complete the catalytic cycle.[7] In addition, a hydrophobic effect may play a role in accelerating this reaction.[2a]

In summary, we developed a novel, efficient, and general aqueous nucleophilic ring-opening reaction of various aziridines and epoxides that proceed with a wide range of nucleophiles in the presence of tributylphosphine, which offers the potential of being both economical and environmentally benign. Further studies of this reaction are in progress.

Experimental Section

General Experimental Conditions. All reactions were performed under an atmosphere of either dry argon or nitrogen using 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. Commercially available reagents were used as received without further purification. Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$. 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 Aqueous Ring Opening of Epoxides 1 or Aziridines 4 with Nucleophile A−G Catalyzed by Bu_3P. To a stirred solution of epoxide **1** or aziridine **4** (0.5 mmol) and nucleophile **A**−**G** (0.55 mmol) was added tributylphosphine (0.014 mL, 0.05 mmol) and water (2.0 mL) under argon, and the resulting mixture was stirred at room temperature for 12 h. The mixture was extracted by CH_2Cl_2 (2 × 5 mL), and the crude product was purified by flash column chromatography to provide the corresponding product.

Procedure of Ring-Opening of Aziridines 4a with Phenol Catalyzed by Bu_3P in Mixed Aqueous/Organic Solvent. To a stirred solution of aziridine **4a** (126 mg, 0.5 mmol) and phenol (52 mg, 0.55 mmol) in 0.2 mL of CH_3CN was added tributylphosphine (0.014 mL, 0.05 mmol) followed by water (2.0 mL) under argon, and the resulting mixture was stirred at room temperature for 12 h. The mixture was extracted by CH_2Cl_2 (2 × 5 mL), and the crude product was purified by flash column chromatography to provide the corresponding product **5aA**.

1-Phenoxymethyl-benzenemethanol (2aA).[14] White solid; mp 62−64 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.80 (d, ^3J = 2.4 Hz, 1H, OH), 3.95−4.03 (m, 1H), 4.07−4.12 (m, 1H), 5.08−5.13 (m, 1H, CH), 6.88−6.95 (m, 3H), 7.23−7.45 (m, 7H); IR (film) $\bar{\nu}$ 3292 (OH), 1598 cm^{-1} (Ph); EI-MS *m*/*z* (%) 214 (20) [M$^+$], 197 (33) [M$^+$ − OH], 108 (100); HRMS calcd for $C_{14}H_{14}O_2$ 214.1034, found 214.1045.

2-Phenoxy-benzeneethanol (3aA).[14] White solid; mp 76−78 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 2.24−2.29 (m, 1H. OH), 3.75−3.94 (m, 2H, CH_2), 5.24 (dd, ^3J = 8.2 Hz, 3.7 Hz, 1H, CH), 6.84−6.87 (m, 3H), 7.14−7.34 (m, 7H); IR (film) $\bar{\nu}$ 3435 (OH), 1594 cm^{-1} (Ph); EI-MS *m*/*z* (%) 214 (1) [M$^+$], 94 (100) [PhOH]; HRMS calcd for $C_{14}H_{14}O_2$ 214.1034, found 214.1039.

1-Phenylthiomethyl-benzenemethanol (2aB).[15] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.86 (s, 1H, OH), 3.08 (dd, ^2J = 13.8 Hz, ^3J = 9.4 Hz, 1H), 3.30 (dd, ^2J = 13.8 Hz, ^3J = 3.6 Hz, 1H), 4.71 (d, ^3J = 9.3 Hz, CH), 7.20−7.42 (m, 10H); EI-MS *m*/*z* (%) 230 (69) [M$^+$], 213 (48) [M$^+$ − OH], 124 (100).

2-Phenylthiobenzeneethanol (3aB).[15] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.13 (s, 1H, OH), 3.88−3.89 (m, 2H, CH_2), 4.29 (t, ^3J = 6.9 Hz, 1H, CH), 7.21−7.42 (m, 10H); EI-MS *m*/*z* (%) 230 (37) [M$^+$], 199 (100) [M$^+$ − CH_3OH].

1-[(4-Methylphenyl)methylthio]methyl-benzenemethanol (2aC). Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.34 (s, 3H, CH_3), 2.66 (dd, ^2J = 13.9 Hz, ^3J = 9.2 Hz, 1H), 2.81 (dd, ^2J = 13.9 Hz, ^3J = 3.7 Hz, 1H), 2.87 (d, ^3J = 2.6 Hz, OH), 3.70 (s, 2H, CH_2), 4.68 (m, ^3J = 9.1, 2.9 Hz, 1H, CH), 7.13−7.36 (m, 9H); IR (film) $\bar{\nu}$ 3430 cm^{-1} (OH), 1514 (Ph), 1381 cm^{-1} (CH_3); EI-MS *m*/*z* (%) 258 (1) [M$^+$], 152 (53) [M$^+$ − C_8H_9], 105 (100); HRMS calcd for $C_{16}H_{18}OS$ 258.1108, found 258.1117. Anal. Calcd for $C_{16}H_{18}SO$: C, 74.38; H, 7.02. Found: C, 74.27; H, 6.98.

2-[(4-Methylphenyl)methylthio]benzeneethanol (3aC). Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.89 (t, ^3J = 6.1 Hz, 1H, OH), 2.32 (s, 3H, CH_3), 3.51 (d, ^2J = 13.4 Hz, 1H), 3.64 (d, ^2J = 13.3 Hz, 1H), 3.78−3.87 (m, 3H), 7.08−7.14 (m, 4H), 7.25−7.34 (m, 5H); IR (film) $\bar{\nu}$ 3399 (OH), 1600 (Ph), 1380 cm^{-1} (CH_3); EI-MS *m*/*z* (%) 258 (8) [M$^+$], 105 (100); HRMS calcd for $C_{16}H_{18}OS$ 258.1108, found 258.1112. Anal. Calcd for $C_{16}H_{18}SO$: C, 74.38; H, 7.02. Found: C, 74.41; H, 7.12.

2-(Phenylthio)cyclohexanol (2bB).[16] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.15−1.45 (m, 4H), 1.60−1.85 (m, 2H), 2.00−2.20 (m, 2H), 2.70 (br, 1H, OH), 2.75−2.90 (m, 1H, CH), 3.30−3.40 (m, 1H, CH), 7.25−7.40 (m, 3H), 7.45−7.60 (m, 2H).

2-(Phenylmethyl)amino-cyclohexanol (2bD).[12] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 0.98 (m, 1H), 1.12−1.30 (m, 3H), 1.60−1.80 (m, 2H), 1.93−2.02 (m, 1H), 2.11−2.20 (m, 1H), 2.32 (ddd, *J* = 11.3, 9.2, 3.8 Hz, 1H), 2.80 (br, 2H), 3.22 (ddd, *J* = 9.2, 9.2, 3.8 Hz, 1H), 3.70 (d, *J* = 12.9 Hz, 1H), 4.00 (d, *J* = 12.9 Hz, 1H), 7.20−7.40 (m, 5H).

2-Phenylamino-1-cyclohexanol (2bE).[11] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.00−1.10 (m, 1H), 1.25−1.41 (m, 3H), 1.70−1.81 (m, 2H), 2.05−2.20 (m, 2H), 3.02 (br s, 2H), 3.13 (ddd, *J* = 11.1, 9.3, 4.0 Hz, 1H), 3.35 (ddd, *J* = 9.7, 9.4, 4.1 Hz, 1H), 6.70−6.85 (m, 3H), 7.10−7.20 (m, 2H); EI-MS *m*/*z* (%) 192 (MH$^+$, 7), 191 (M$^+$, 43), 174 (1), 148 (13), 132 (100), 118(25), 106 (35), 93(11,), 77(14).

2-(Phenylthio)cyclopentanol (2cB).[15] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.50−1.70 (m, 2H), 1.70−1.90 (m, 3H), 2.01−2.15 (m, 1H), 2.20−2.30 (m, 1H), 3.30−3.45 (m, 1H), 4.10−4.20 (m, 1H), 7.20−7.30 (m, 3H), 7.35−7.50 (m, 2H); EI-MS *m*/*z* (%) 195 (MH$^+$, 13), 194 (M$^+$, 100), 110 (91).

2-(Phenylamino)cyclopentanol (2cE).[11] White solid; mp 57−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.35−1.45 (m, 1H), 1.60−1.65 (m, 1H), 1.68−1.84 (m, 2H), 1.86−2.01 (m, 1H), 2.10−2.20 (m, 1H), 2.40−3.10 (br, 2H), 3.55−3.65 (m, 1H), 4.00−4.10 (m, 1H), 6.65−6.80 (m, 3H), 7.10−7.25 (m, 2H).

3-(Phenylthio)-2-butanol (2dB).[17] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.25 (d, *J* = 6.3 Hz, 3H), 1.30 (d, *J* = 6.9 Hz, 3H), 2.30 (br, 1H), 3.10−3.20 (m, 1H), 3.60−3.75 (m, 1H), 7.20−7.30 (m, 3H), 7.35−7.50 (m, 2H); MS *m*/*z* (%) 183 (MH$^+$, 17), 182 (M$^+$, 100), 137 (96).

3-Phenylamino-2-butanol (2dE).[18] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.15 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 2.60 (br, 1H), 3.30−3.40 (m, 1H), 3.60−3.70 (m, 1H), 6.65−6.85 (m, 3H), 7.20 (m, 2H).

1-Phenylthio-2-hexanol (2eB).[19] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.26−1.56 (m, 6H), 2.60 (br s, 1H), 2.84 (dd, *J* = 13.6, 8.5 Hz, 1H), 3.14 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.62−3.67 (m, 1H), 7.18−7.38 (m, 5H); EI-MS *m*/*z* (%) 210 (M$^+$, 24), 124 (100).

***N*-(2-Phenoxyl)cyclohexyl-4-methylbenzensulfonamide (5aA).**[7] White solid; mp 146−148 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.25−1.33 (m, 4H, CH_2CH_2), 1.56−1.75 (m, 2H, CH_2), 2.02−2.05 (m, 1H), 2.21−2.24 (m, 1H), 2.43 (s, 3H, CH_3), 3.27−3.40 (m, 1H, CH), 4.11−4.25 (m, 1H, CH), 4.76 (d, ^3J(H,H) = 3.6 Hz, 1H, NH), 6.67 (d, ^3J(H,H) = 8.2 Hz, 2H), 6.94 (t, ^3J(H,H) = 7.5 Hz, 1H,), 7.21−7.30 (m, 4H), 7.76 (d, ^3J(H,H) = 8.2 Hz, 2H); IR (film) $\bar{\nu}$ 3297 (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-Phenylthiocyclohexyl)-4-methylbenzenesulfonamide (5aB).**[7] 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, CH_3), 2.80−3.00 (m, 2H), 5.10−5.20 (d, ^3J = 3.6 Hz, 1H, NH), 7.20−7.40 (m, 7H), 7.75 (d, ^3J = 8.3 Hz, 2H); IR (film) $\bar{\nu}$ 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.

***N*-2-((4-Methylphenyl)methylthio)cyclohexyl)-4-methylbenzenesulfonamide (5aC).**[7] White solid; mp 87−89 °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, CH_3), 2.33−2.38 (m, 1H, CH), 2.41 (s, 3H, CH_3), 2.78−2.92 (m, 1H, CH), 3.45−3.57 (m, 2H, CH_2), 5.03 (d, ^3J = 2.4 Hz, 1H), 7.10−7.30 (m, 6H), 7.74−7.77 (d, ^3J = 8.2 Hz); IR (film) $\bar{\nu}$ 3309 (NH), 1597 (Ph), 1383 cm^{-1} (CH_3); EI-MS *m*/*z* (%) 389 (1) [M$^+$], 234 (100); HRMS calcd for $C_{21}H_{27}NS_2O_2$ 389.1449, found 389.1456.

***N*-(2-Phenylmethylamino)cyclohexyl-4-methylbenzenesulfonamide (5aD).**[7] ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 1.06−1.41 (m, 6H), 156−1.63 (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, CH), 3.59 (d, ^3J = 13.2 Hz, 1H, CH), 3.75, (d, ^3J = 13.1 Hz, 1H, CH), 7.21−7.36 (m, 7H), 7,74 (d, ^3J = 8.2 Hz, 2H); EI-MS *m*/*z* (%) 359 (MH$^+$ 87), 91 (100).

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***N*-(2-Phenylamino)cyclohexyl-4-methylbenzenesulfonamide (5aE).**[7] ^{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, CH_3), 2.85−3.05 (m, 3H), 5.08 (br, 1H, NH), 6.45 (d, ^3J = 7.4 Hz, 2H), 6.38−6.5 (m, 1H), 7.05−7.30 (m, 4H), 7.81 (d, ^3J = 7.3 Hz, 2H); EI-MS *m*/*z* (%) 344 (20) [M^+], 96 (100).

***N*-[2-(1-Methylethylamino)]cyclohexyl-4-methylbenzenesulfonamide (5aF).**[7] White solid; mp: 112−114 °C; ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C, TMS) δ 0.94 (dd, ^3J = 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, CH_3), 2.45−2.47 (m, 1H), 2.86 (m, 1H), 5.68 (br, 1H, NH), 7.30 (d, ^3J = 8.1 Hz, 2H), 7.76 (d, ^3J = 8.2 Hz, 2H); IR (film) $\bar{\nu}$ 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.

***N*-[2-(1,1-Dimethyl)ethylthio]cyclohexyl-4-methylbenzenesulfonamide (5aG).**[7] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.29 (s, 9H, $C(CH_3)_3$), 1.45−1.67 (m, 6H), 2.04−2.17 (m, 2H), 2.42 (s, 3H, CH_3), 2.43−2.58 (m, 1H, CH), 2.59−2.81 (m, 1H, CH), 5.37 (br, 1H, NH), 7.30 (d, ^3J = 7.9 Hz, 2H), 7.76 (d, ^3J = 8.0 Hz, 2H); IR (film) $\bar{\nu}$ 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 calcd for $C_{17}H_{27}NS_2O_2$ 341.1407, found 341.1510.

1-(Phenylthio)methyl-*S*-(4-methylphenyl)benzenemethansulfonamide and 2-Phenylthio-*S*-(4-methylphenyl)benzeneethansulfonamide (5bB and 6bB).[7] Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.18−3.22 (m, 2H, CH_2), 3.34−3.39 (m, 2H, CH_2), 4.13 (t, ^3J = 7.2 Hz, 1H, CH), 4.30 (q, ^3J = 6.7 Hz, 1H, CH), 4.74 (br, 1H, NH), 5.33 (br, 1H, NH), 7.08−7.27 (m, 24H), 7.50 (d, ^3J = 8.2 Hz, 2H), 7.64 (d, ^3J = 8.2 Hz, 2H); IR (film) $\bar{\nu}$ 3290 (NH), 1599 cm^{-1}(Ph); EI-MS *m*/*z* (%) 383 (2), [M^+], 260 (100). 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)benzenemethanamine (5cB).**[7] Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, 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 (m, 10H); IR (film) $\bar{\nu}$ 3280 (NH), 1583 cm^{-1} (Ph); EI-MS *m*/*z* (%) 297 (2), [M^+], 188 (24) [$M^+ - PhSH$]; HRMS calcd for $C_{19}H_{23}NS$ 297.1551, found 297.1507.

***N*-Phenyl-N′-benzyl-1,2-cyclohexanediamine (5cE).**[7] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 1.10−1.13 (m, 1H), 1.20−1.23 (m, 3H), 1.70−1.72 (m, 2H), 2.10 (br s, 1H), 2.18 (m, 2H), 2.33 (ddd, J = 9.9, 9.9, 4.2 Hz, 1H), 3.12 (ddd, J = 10.2, 10.2, 3.6 Hz, 1H), 3.37 (br s, 1H), 3.80 (AB, J = 13.5 Hz, 2H), 6.64 (m, 3H), 7.13 (m, 2H), 7.25 (m, 5H); EI-MS *m*/*z* (%) 281 (23) [MH^+].

The Preparation of Phosphonium Salt 7. To a mixture of Bu_3P (0.26 mL, 1 mmol) with aziridine **4a** (252 mg, 1 mmol) was added 4 mL of water. The mixture was then stirred for 48 h at room temperature. After the addition of 60% aqueous perchloric acid (2 mL) CH_2Cl_2 (10 mL) was added, and the resulting mixture was cooled at 0 °C to give some solid. After recrystallization from CH_2Cl_2, a good crystal could be obtained in 26% 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 (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.

Reaction of 4a with Nucleophile C in the Presence of Phsphonium 7. To a stirred solution of **7** (28 mg, 0.05 mmol) in THF (0.2 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 for 15 min, then **4a** (126 mg, 0.5 mmol) and C (0.03 mL 0.5 mmol) were added. The mixture was warmed to room temperature and then stirred for 48 h. The mixture was extracted by CH_2Cl_2 (2 × 5 mL) and the crude product was purified by flash column chromatography to provide corresponding product **5aC** in 48% yield.

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