

## Research Article

# A Remarkably Efficient Phase-Transfer Catalyzed Amination of $\alpha$ -Bromo- $\alpha$ , $\beta$ -Unsaturated Ketones in Water

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Tandem conjugate addition-alkylation reaction of various amines with  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones resulted in near-quantitative conversions into the corresponding aziridines when the reaction was carried out in the presence of 10 mol% of phase-transfer, PT catalysts in water. Some chiral quaternary ammonium salts derived from *Cinchona* alkaloids were investigated as water-stable PT catalysts. The scope and limitations of the reaction have also been investigated. The catalytic performances were significantly improved in comparison with the corresponding ordinary quaternary ammonium salt catalysts, and excellent yields (81%–96%) were obtained. Although an increase in the rate of aziridination has been accomplished, no stereoselectivity was observed. The positive values of the protocol have been confirmed.

## 1. Introduction

Small heterocyclic ring systems are of a high importance in theoretical and synthetic organic, bioorganic, and medicinal chemistry. Particularly, aziridines are highly valuable nitrogen containing heterocyclic compounds and are interesting systems as they occur in a number of natural and biologically active substances [1, 2]. It is worth mentioning that there are several important natural products that contain the aziridine moiety such as mitomycin C, miraziridine A, maduropeptin, porfiromycin, and carzinophilin A [3]. A number of saccharide derivatives containing the aziridine group have been made, mostly as intermediates, but also as glycosidase inhibitors [2–4].

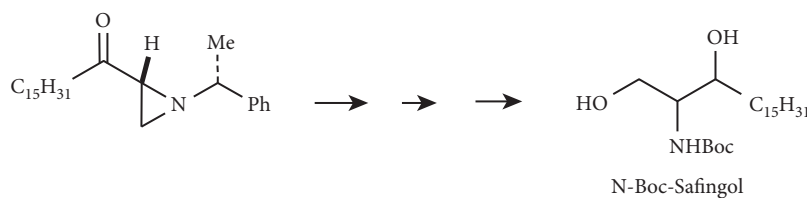
Due to their proton-accepting properties, rigidity, and potential reactivity, they undergo specific molecular interactions with proteins. They are versatile reaction intermediates and useful substrates for a variety of ring-cleavage and ring-expansion reactions. They can be used as precursors to amines, amino alcohols, diamines, and other useful nitrogen containing molecules [1, 2].

The development of efficient and stereoselective methods for synthesis of aziridines is a big challenge in organic

synthesis. Notwithstanding, numerous synthetic routes are available for the preparation of aziridines, and there are a few examples of bicyclic- $\alpha$ -ketoaziridine synthesis [3]. However, they have a great potential to be used as synthetic intermediates for the preparation of several antibiotics [1, 5].

Thus, bicyclic  $\alpha$ -keto aziridines represent an important class of compounds since they may be considered simultaneously as  $\alpha$ - or  $\beta$ -amino acid derivatives. The active keto-derivatives bearing Lewis basic oxygen readily participate in a tandem process to deliver both  $\alpha$ - and  $\beta$ -substituted threo- $\alpha$ -hydroxy- $\beta$ -amino acids in an orthogonally protected form. Particularly, this procedure has been used to prepare erythro-1, 2-amino alcohols and 2-amino-1, 3-diols with high diastereoselectivities and chemical yields from highly stereoselective carbonyl group reduction of 2-acylaziridines (Scheme 1) [6]. Another problem is that aziridine moieties are often introduced after multistep syntheses, and thus, direct aziridination is a goal of considerable importance in organic chemistry [2, 7]. Moreover, convenient protocols that afford optically active aziridines are of a high value to the academic, natural product, agrochemical, pharmaceutical, and medicinal chemistry communities [8–10].

Quite recently, we have reported the catalytic and highly efficient synthesis of bicyclic- $\alpha$ -ketoaziridines through



SCHEME 1

successive processes of addition, proton transfer, and intramolecular alkylation with various primary aliphatic amines using ordinary PT catalyst, which allows it to be a practical method (Scheme 2) [5]. In continuation of the previous work, this experiment was designed for the purpose of thorough investigation of the scope and generality of the protocol using chiral PT catalysts and additional substrates and reagents.

## 2. Experimental Section

All  $^1\text{H}$  and  $^{13}\text{C}$ NMR spectra were recorded on a JEOL JNM-EX 400 FT-NMR system using  $\text{CDCl}_3$  as a solvent at room temperature. Chemical shifts are given in ppm and J-values in Hz. Matrix silica (Si-60A° 35–70  $\mu\text{m}$ ) was used to perform flash chromatography. GLC analyses were carried out on a Varian 3300 chromatograph equipped with split injector, FID detector, and a Varian 4400 integrator. Percoated (0.25 mm) Merck silica gel F-254 plates were used to do analytical TLC. IR spectra were recorded on a FT-IR spectrometer and are reported as wave number. GC-MS spectra were registered on a Hewlett 5890 Packard series II CP Sil 5CB column (25 m) followed by VG Quattro mass spectrometer. All reagents and solvents except  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones, **1a–c**, were obtained from commercial sources and used as received without further purification. All  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones, **1a–c**, were prepared according to literature procedure [11].

**2.1. General Procedure for the Reaction of 2-Bromo Enones (1a–c) with Various Amines (2a–g) Catalyzed by 10 mol% II.** The reaction was carried out by mixing  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones (1.25 mmol), catalysts (10 mmol%) and amines (1.0 mmol) in  $\text{H}_2\text{O}$  (5 mL) and stirred at room temperature until the reactants were consumed (see Table 1). The crude reaction mixture was extracted with  $\text{Et}_2\text{O}$  (3x5 mL), and the combined organic layers were dried using  $\text{Na}_2\text{SO}_4$ . The solvent was removed using evaporator under reduced pressure. Flash chromatography on silica gel was performed (pentane/diethyl ether, 4:1) to get the expected products (**3**, **4**, and **5**) in near-quantitative yields. All the products were characterized by GC-MS and  $^1\text{H}$  and  $^{13}\text{C}$  NMR analysis, and their spectral data are given below [5, 12].

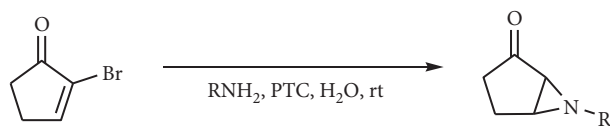
**2.2. 6-((S)-1-Phenylethyl)-6-aza-bicyclo[3.1.0]hexan-2-one (3g).** (0.165 g, 82%, 65:34) as a yellow oil,  $R_f$  0.41 (3:7  $\text{Et}_2\text{O}$ /pentane);  $[\alpha]_D^{22} = -41$  and  $-26.5^\circ$  ( $c = 1.0$ ,  $\text{CH}_2\text{Cl}_2$ ); IR (neat, NaCl plates,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3050, 2952, 1728, 1685, 1637, 1410, 1332;  $^1\text{H}$ NMR diastereomer A:  $\delta$  1.30 (d,  $J = 6.4$  Hz,

3H), 1.72–2.05 (m, 2H), 2.13 (d,  $J = 4.0$  Hz, 1H), 2.24–2.36 (m, 2H), 2.46 (t,  $J = 3.6$  Hz, 1H), 2.55 (q,  $J = 6.4$  Hz, 1H), 7.18–7.25 (m, 3H), 7.38–7.45 (m, 2H); diastereomer B:  $\delta$  1.49 (d,  $J = 6.4$  Hz, 3H), 1.98–2.06 (m, 2H), 2.10 (d,  $J = 4.4$  Hz, 1H), 2.28–2.46 (m, 2H), 2.72 (q,  $J = 6.8$  Hz, 1H), 2.79 (t,  $J = 3.2$  Hz, 1H), 7.20–7.26 (m, 3H), 7.27–7.34 (m, 2H);  $^{13}\text{C}$ NMR:  $\delta$  211.9 (CO), 143.5 (C), 128.2 (CH), 127.2 (CH), 126.3 (CH), 66.8 ( $\text{CH}_2\text{Ph}$ ), 47.5 (CH), 46.2 (CH), 32.7 ( $\text{CH}_2$ ), 24.4 ( $\text{CH}_2$ ), 23.9 ( $\text{CH}_3$ ); MS (GC-MS):  $m/z$  201 ( $\text{M}^+$ , 1), 106 (13), 105 (100), 97 (17), 79 (12), 77 (15), 51 (5), 42 (6).

**2.3. 7-Benzyl-7-aza-bicyclo[4.1.0]heptan-2-one (4a).** (0.195 g, 97%) as a brown oil,  $R_f$  0.43 (3:7  $\text{Et}_2\text{O}$ /pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3023, 2905, 1715, 15981, 1492, 1428, 1324;  $^1\text{H}$ NMR:  $\delta$  1.45–1.85 (m, 2H), 1.98–2.24 (m, 2H), 2.26–2.42 (m, 2H), 2.39 (d,  $J = 7.4$  Hz, 1H), 2.50–2.73 (m, 1H), 3.40 (d,  $J = 13.6$  Hz, 1H), 3.84 (d,  $J = 14.0$  Hz, 1H), 7.43–7.52 (m, 5H);  $^{13}\text{C}$ NMR:  $\delta$  208.0 (CO), 138.5 (C), 128.5 (CH), 127.8 (CH), 127.0 (CH), 65.3 ( $\text{CH}_2\text{Ph}$ ), 46.4 (CH), 44.6 (CH), 34.8 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 18.5 ( $\text{CH}_2$ ); MS (GC-MS):  $m/z$  202 ( $\text{M}^+$ , 1), 201 (2), 110 (13), 104 (11), 92 (15), 91 (100), 65 (12).

**2.4. 7-Furan-2-ylmethyl-7-aza-bicyclo[4.1.0]heptan-2-one (4b).** (0.181 g, 95%) as a brown oil,  $R_f$  0.46 (3:7  $\text{Et}_2\text{O}$ /pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3053, 2867, 1704, 14935, 1392;  $^1\text{H}$ NMR:  $\delta$  1.38–1.58 (m, 2H), 1.63–1.79 (m, 2H), 1.85–2.10 (m, 2H), 2.34 (d,  $J = 6.8$  Hz, 1H), 2.40–2.44 (m, 1H), 3.60 (d,  $J = 14.0$  Hz, 1H), 4.27 (d,  $J = 13.6$  Hz, 1H), 6.10 (dd,  $J = 3.2$  and 2.4 Hz, 1H), 6.21 (d,  $J = 2.4$  Hz, 1H), 7.26 (d,  $J = 7.2$  Hz, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.4 (CO), 144.3 (C), 112.3 (CH), 108.5 (CH), 106.6 (CH), 57.8 ( $\text{CH}_2$ ), 47.6 (CH), 44.8 (CH), 39.1 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 20.3 ( $\text{CH}_2$ ); MS (GC-MS):  $m/z$  191 ( $\text{M}^+$ , 1), 82 (24), 81 (100), 53 (15).

**2.5. 7-Cyclohexyl-7-aza-bicyclo[4.1.0]heptan-2-one (4c).** (0.189 g, 98%) as a brown oil,  $R_f$  0.61 (3:7  $\text{Et}_2\text{O}$ /pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 2902, 1698, 1420, 1320, 1330;  $^1\text{H}$ NMR:  $\delta$  1.12–1.22 (m, 4H), 1.26–1.42 (m, 4H), 1.50–1.62 (m, 2H), 1.78 (d,  $J = 9.2$  Hz, 1H), 1.88–1.95 (m, 2H), 1.97–2.02 (m, 2H), 2.04–2.07 (m, 1H), 2.16–2.22 (m, 2H), 2.36–2.48 (m, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.5 (CO), 68.3 (CH), 46.6 (CH), 42.3 (CH), 37.0 ( $\text{CH}_2$ ), 34.2 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_2$ ), 27.5 ( $\text{CH}_2$ ), 25.7 ( $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ); MS (GC-MS):  $m/z$  194 ( $\text{M}^+ + \text{H}$ , 2), 193 ( $\text{M}^+$ , 17), 150 (100), 112 (16), 83 (17), 67 (17), 56 (42), 42 (26).



SCHEME 2

TABLE 1: **II** catalyzed aziridination of **1a–c** with amines (Scheme 5) and **2a–g** to give structures **3a–g**, **4a–g**, and **5a–f**, respectively, in H<sub>2</sub>O at room temperature.

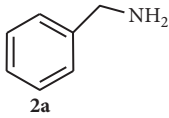
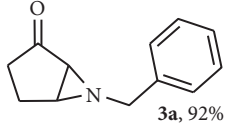
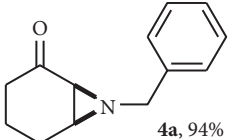
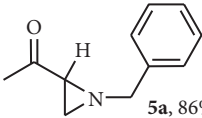
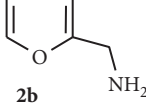
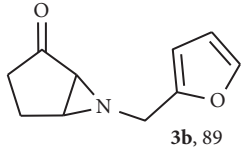
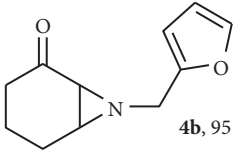
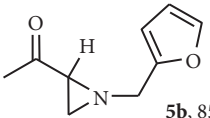
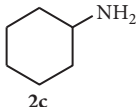
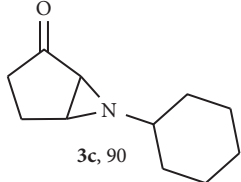
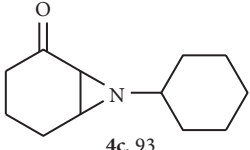
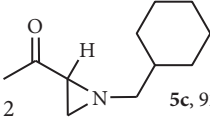
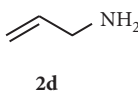
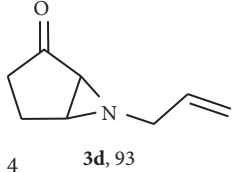
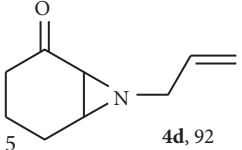
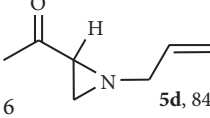
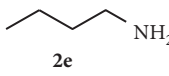
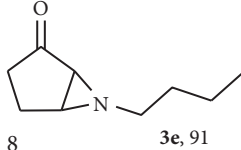
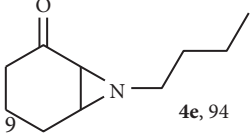
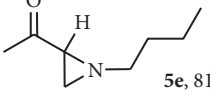
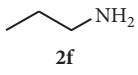
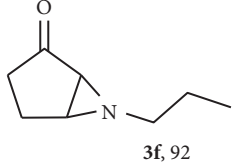
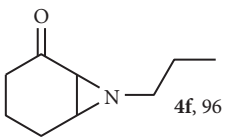
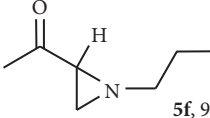
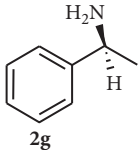
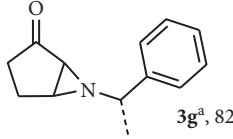
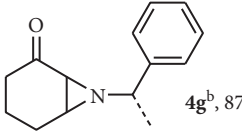
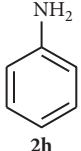
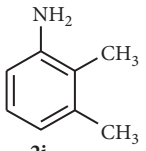
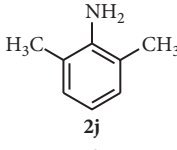
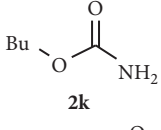
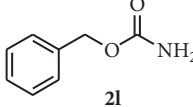
Entry	Amines	Time (h)	Products and yields (%)		
			3	4	5
1.	 <b>2a</b>	2	 <b>3a</b> , 92%	 <b>4a</b> , 94%	 <b>5a</b> , 86%
2.	 <b>2b</b>	3	 <b>3b</b> , 89	 <b>4b</b> , 95	 <b>5b</b> , 85
3.	 <b>2c</b>	1.5	 <b>3c</b> , 90	 <b>4c</b> , 93	 <b>5c</b> , 92
4.	 <b>2d</b>	1	 <b>3d</b> , 93	 <b>4d</b> , 92	 <b>5d</b> , 84
5.	 <b>2e</b>	1	 <b>3e</b> , 91	 <b>4e</b> , 94	 <b>5e</b> , 81
6.	 <b>2f</b>	1	 <b>3f</b> , 92	 <b>4f</b> , 96	 <b>5f</b> , 93
7.	 <b>2g</b>	4	 <b>3g<sup>a</sup></b> , 82	 <b>4g<sup>b</sup></b> , 87	—
8.	 <b>2h</b>	—	—	—	—

TABLE 1: Continued.

Entry	Amines	Time (h)	Products and yields (%)		
			3	4	5
9			—	—	—
10.			—	—	—
11.			—	—	—
12.			—	—	—

2.6. 7-Allyl-7-aza-bicyclo[4.1.0]heptan-2-one (4d). (0.139 g, 92%) as a brown oil,  $R_f$  0.57 (1 : 9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 3045, 2910, 1721, 1439; <sup>1</sup>HNMR:  $\delta$  1.50–1.70 (m, 2H), 1.75–1.84 (m, 2H), 1.88–2.10 (m, 2H), 2.11 (d,  $J$  = 6.0 Hz, 1H), 2.35–2.51 (m, 1H), 2.91 (d,  $J$  = 5.6 Hz, 1H), 3.09 (d,  $J$  = 5.6 Hz, 1H), 5.14 (dd,  $J$  = 9.2, 1.2 Hz, 1H), 5.23 (dd,  $J$  = 15.6, 1.6 Hz, 1H), 5.57–5.90 (m, 1H); <sup>13</sup>CNMR:  $\delta$  208.0 (CO), 135.4 (CH<sub>2</sub>), 127.5 (CH), 62.3 (CH<sub>2</sub>), 46.4 (CH), 43.1 (CH<sub>2</sub>), 37.3 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 19.8 (CH<sub>2</sub>); MS (GC-MS):  $m/z$ % 152 (M<sup>+</sup>+H, 4), 151 (M<sup>+</sup>, 35), 122 (49), 95 (81), 94 (100), 80 (63), 67 (38), 54 (53).

2.7. 7-Butyl-7-aza-bicyclo[4.1.0]heptan-2-one (4e). (0.157 g, 94%) as a brown oil,  $R_f$  0.63 (1 : 9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 2950, 1708, 1470, 1327; <sup>1</sup>HNMR:  $\delta$  0.89 (t,  $J$  = 7.2 Hz, 3H), 1.30–1.42 (m, 2H), 1.46–1.60 (m, 2H), 1.66–1.76 (m, 2H), 1.88 (d,  $J$  = 5.6 Hz, 1H), 1.96–2.00 (m, 2H), 2.02–2.19 (m, 2H), 2.22–2.30 (m, 2H), 2.36–2.45 (m, 1H); <sup>13</sup>CNMR:  $\delta$  208.2 (CO), 61.0 (CH<sub>2</sub>), 47.3 (CH), 44.6 (CH), 37.2 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>), 21.6 (CH<sub>2</sub>), 19.7 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>); MS (GC-MS):  $m/z$ % 168 (M<sup>+</sup>+H, 2), 167 (M<sup>+</sup>, 5), 138 (32), 97 (100), 96 (53), 83 (24), 69 (62), 55 (58).

2.8. 7-Propyl-7-aza-bicyclo[4.1.0]heptan-2-one (4f). (0.150 g, 98%) as a brown oil,  $R_f$  0.63 (1 : 9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 2958, 1706, 1481, 1325; <sup>1</sup>HNMR:  $\delta$  0.89 (t,  $J$  = 7.2 Hz, 3H), 1.50–1.62 (m, 2H), 1.65–1.78 (m, 2H), 1.90 (d,  $J$  = 5.2 Hz, 1H), 1.95–2.02 (m, 2H), 2.04–2.11 (m, 2H), 2.12–2.28 (m, 2H), 2.36–2.47 (m, 1H); <sup>13</sup>CNMR:  $\delta$  207.5 (CO), 61.2 (CH<sub>2</sub>), 45.6 (CH), 43.3 (CH), 36.5 (CH<sub>2</sub>), 21.5 (CH<sub>2</sub>), 21.0 (CH<sub>2</sub>), 18.9 (CH<sub>2</sub>), 12.0 (CH<sub>3</sub>); MS (GC-MS):  $m/z$ % 154 (M<sup>+</sup>+H, 2), 153 (M<sup>+</sup>, 1), 124

(4), 124 (48), 97 (41), 96 (100), 83 (46), 68 (72), 55 (96), 41 (76).

2.9. 7-((S)-1-Phenylethyl)-7-aza-bicyclo[4.1.0]heptan-2-one (4g). (0.187 g, 87%, 53 : 27) as a brown oil,  $R_f$  0.38 (3 : 7 Et<sub>2</sub>O/pentane);  $[\alpha]_D^{22}$  = -64.3 and -16.7° ( $c$  = 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 3025, 2965, 1721, 1622, 1561, 1425, 1339; <sup>1</sup>HNMR: as a mixture of two diastereomers: isomer C:  $\delta$  1.64 (d,  $J$  = 6.8 Hz, 3H), 1.80–1.95 (m, 2H), 2.03–2.26 (m, 2H), 2.28–2.45, (m, 2H), 2.61 (d,  $J$  = 8.2 Hz, 1H), 2.70 (q,  $J$  = 6.2 Hz, 1H), 3.96 (t,  $J$  = 6.0 Hz, 1H), 7.40–7.70 (m, 5H), isomer D:  $\delta$  1.62 (d,  $J$  = 6.8 Hz, 3H), 1.80–1.95 (m, 2H), 2.03–2.26 (m, 2H), 2.28–2.45, (m, 2H), 2.61 (d,  $J$  = 8.2 Hz, 1H), 2.85 (t,  $J$  = 6.8 Hz, 1H), 2.91 (q,  $J$  = 6.4 Hz, 1H), 7.40–7.72 (m, 5H); <sup>13</sup>CNMR:  $\delta$  208.3 (CO), 151.2 (C), 129.1 (CH), 127.8 (CH), 125.9 (CH), 69.2 (-CHPh), 46.4 (CH), 44.6 (CH), 29.4 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 24.3 (CH<sub>2</sub>), 20.1 (CH<sub>3</sub>); MS (GC-MS):  $m/z$ % 215 (M<sup>+</sup>, 1), 111 (31), 105 (100), 77 (13).

2.10. 1-(1-Benzylaziridin-2-yl) Ethanone (5a). (0.151 g, 86%) as a brown oil,  $R_f$  0.46 (1 : 9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 3020, 2985, 1710, 1601, 1425, 1380, 1228; <sup>1</sup>HNMR:  $\delta$  1.80 (dd,  $J$  = 6.1, 2.4 Hz, 2H), 2.07 (s, 3H), 2.33 (m, 1H), 3.59 (d,  $J$  = 13.6 Hz, 1H), 3.71 (d,  $J$  = 13.2 Hz, 1H), 7.55–7.62 (m, 5H); <sup>13</sup>CNMR:  $\delta$  208.3 (CO), 148.5 (C), 139.8 (CH), 138.5 (CH), 137.8 (CH), 64.4 (CH<sub>2</sub>), 45.7 (CH), 35.9 (CH<sub>2</sub>), 25.5 (CH<sub>3</sub>); MS (GC-MS):  $m/z$ % 175 (M<sup>+</sup>, 2), 132 (17), 92 (10), 91 (100), 65 (9).

2.11. 1-(1-Furan-2-ylmethylaziridin-2-yl) Ethanone (5b). (0.140 g, 85%) as a brown oil,  $R_f$  0.56 (1 : 9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\max}$ , cm<sup>-1</sup>): 3055, 2954, 1702, 1599, 1420, 1356, 1158, 1105; <sup>1</sup>HNMR:  $\delta$  1.73 (d,  $J$  = 6.8 Hz, 2H), 2.06 (s,

3H), 2.20–2.38 (m, 1H), 3.56 (s, 2H), 6.13 (dd,  $J = 3.2, 0.8$  Hz, 2H), 7.16 (d,  $J = 2.8$  Hz, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.5 (CO), 150.5 (C), 142.6 (CH), 110.2 (CH), 108.4 (CH), 56.7 (CH<sub>2</sub>), 45.8 (CH), 34.6 (CH<sub>2</sub>), 25.2 (CH<sub>3</sub>); MS (GC-MS):  $m/z\%$  166 (M<sup>+</sup>+H, 3), 165 (M<sup>+</sup>, 19), 122 (11), 82 (16), 81 (100), 53 (50), 43 (24).

**2.12. 1-(1-Cyclohexylaziridin-2-yl) Ethanone (5c).** (0.154 g, 92%) as a brown oil,  $R_f$  0.76 (1:9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ , cm<sup>-1</sup>): 2992, 1703, 1601, 1420, 1358;  $^1\text{H}$ NMR:  $\delta$  1.70–1.95 (m, 10H), 2.06 (s, 3H), 2.09–2.38 (m, 1H), 2.42–2.54 (m, 2H), 2.68–2.81 (m, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.6 (CO), 69.3 (CH), 44.7 (CH), 34.5 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 16.7 (CH<sub>3</sub>); MS (GC-MS):  $m/z\%$  168 (M<sup>+</sup>+H, 3), 167 (M<sup>+</sup>, 1), 125 (11), 124 (81), 84 (20), 83 (100), 55 (88), 42 (46).

**2.13. 1-(1-Allylaziridin-2-yl) Ethanone (5d).** (0.105 g, 84%) as a brown oil,  $R_f$  0.78 (1:9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ , cm<sup>-1</sup>): 3062, 2982, 1712, 1410, 1350;  $^1\text{H}$ NMR:  $\delta$  1.67 (t,  $J = 6.0$  Hz, 2H), 2.04 (s, 3H), 2.08–2.10 (m, 1H), 2.91 (d,  $J = 5.6$  Hz, 1H), 2.97 (d,  $J = 5.6$  Hz, 1H), 5.13 (d,  $J = 10.4$  Hz, 1H), 5.21 (dd,  $J = 6.0, 1.2$  Hz, 1H), 5.86–5.93 (m, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.2 (CO), 134.6 (CH), 117.3 (CH<sub>2</sub>), 63.1 (CH<sub>2</sub>), 45.4 (CH), 34.5 (CH<sub>2</sub>), 25.3 (CH<sub>3</sub>); MS (GC-MS):  $m/z\%$  125 (M<sup>+</sup>, 4), 124 (9), 110 (11), 84 (30), 82 (100), 71 (43), 55 (51), 54 (73), 43 (73), 42 (69).

**2.14. 1-(1-Butylaziridin-2-yl) Ethanone (5e).** (0.110 g, 81%) as a brown oil,  $R_f$  0.83 (1:9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ , cm<sup>-1</sup>): 2980, 1715, 1461, 1353;  $^1\text{H}$ NMR:  $\delta$  0.94 (t,  $J = 7.2$  Hz, 3H), 1.36–1.44 (m, 2H), 1.52–1.60 (m, 2H), 1.63 (d,  $J = 6.8$  Hz, 2H), 2.05 (s, 3H), 2.24–2.30 (m, 2H), 2.34–2.43 (m, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.6 (CO), 61.2 (CH<sub>2</sub>), 45.4 (CH), 35.7 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 25.4 (CH<sub>3</sub>), 21.6 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>); MS (GC-MS):  $m/z\%$  142 (M<sup>+</sup>+H, 13), 141 (M<sup>+</sup>, 3), 140 (25), 126 (84), 98 (100), 84 (71), 71 (72), 57 (86), 44 (74).

**2.15. 1-(1-Propylaziridin-2-yl) Ethanone (5f).** (0.118 g, 93%) as a brown oil,  $R_f$  0.89 (1:9 Et<sub>2</sub>O/pentane); IR (neat, NaCl plates,  $\nu_{\text{max}}$ , cm<sup>-1</sup>): 2991, 1712, 1456, 1342, 1210;  $^1\text{H}$ NMR:  $\delta$  0.94 (t,  $J = 7.6$  Hz, 3H), 1.42–1.47 (m, 2H), 1.57 (d,  $J = 7.6$  Hz, 2H), 2.03 (s, 3H), 2.21–2.38 (m, 2H), 2.40–2.53 (m, 1H);  $^{13}\text{C}$ NMR:  $\delta$  208.5 (CO), 63.2 (CH<sub>2</sub>), 45.4 (CH), 35.8 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 24.3 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>); MS (GC-MS):  $m/z\%$  127 (M<sup>+</sup>, 8), 126 (33), 112 (22), 98 (89), 84 (100), 71 (81), 56 (78), 42 (76).

### 3. Results and Discussion

For this study, three  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones (1a–c) (Figure 1), several amines (primary, secondary, and aromatic amines) (Figure 2), and three *Cinchona* alkaloid chlorides as PT catalysts (Figure 3) were taken. In order to establish the best protocol, compounds 1a and 2a were used as model reagents. Different solvents such as toluene, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, CH<sub>3</sub>CN, THF, CH<sub>3</sub>OH, and water were

used. The presence of PT catalyst was found to be vital to promote the reactions.

A comparative study among quaternary ammonium catalysts was performed. To achieve an increased conversion rate, we examined the effects of three different PT catalysts derived from salts of *Cinchona* alkaloid, and their effect was compared with tetrabutylammonium bromide, TBAB. Salts of *Cinchona* alkaloid catalysts were chosen since ordinary tetraalkyl quaternary salts are less stable at high temperatures or highly alkaline conditions. Other than having the beneficial characteristics of a good phase transfer catalyst, they are also usually inexpensive [13].

Above and beyond, we choose *Cinchona* alkaloid chlorides for four reasons. First, they are highly lipophilic as PT catalyst. Second, the secondary 9-OH group can serve as a Lewis acid (hydrogen bond donor), which assists conjugate addition through coordination with the carbonyl oxygen of the substrate (Scheme 3). In other words, both the substrate and reagent can synergistically be activated by the catalyst. Third, the cinchoninium cation, Q<sup>+</sup>, can act as Lewis acid and coordinates with the carbonyl oxygen of the enone to facilitate initial addition of the amine (Scheme 4). Finally, the reaction could be enantioselective since catalysts are chiral. It is believed that the active sites in salts of *Cinchona* alkaloids (9-OH, Q<sup>+</sup>, and the ring) act in catalysis not independently but cooperatively and simultaneously [14–16]. In general, the alkylation reaction was proposed to proceed through an ion-pair complex between the cinchoninium cation, Q<sup>+</sup>, and the anionic nucleophile, which could be stabilized through hydrogen bonding and  $\pi$ - $\pi$  stacking interactions [1].

Three different catalysts, *N*-benzyl cinchoninium chloride **I**, *N*-benzyl cinchonidinium chloride **II**, and *N*-benzyl quininium chloride **III**, were employed. Water was used as the solvent, and the reactions were run at room temperature. When **2a** was reacted with **1a** in the presence of the aforementioned catalysts, **3a** was isolated in 88%, 91%, and 83% yield, respectively, after 2 h of reaction. This indicated that all the catalysts employed have similar activity. Chlorides of *Cinchona* alkaloids showed superior activity compared with ordinary quaternary ammonium chlorides (Bu<sub>4</sub>NCl, benzyltriethylammonium chloride) [5]. This is also true for other ordinary quaternary ammonium catalysts (Bu<sub>4</sub>NBr, Bu<sub>4</sub>NI, Bu<sub>4</sub>NBF<sub>4</sub>, and Hex<sub>4</sub>NBr). We found that a combination of water and salts of *Cinchona* alkaloids catalyst was effective, giving tandem reaction in reduced reaction times, in good yield.

Finally, to explore the scope and generality of this method, structurally different acceptors, namely,  $\alpha$ -bromo-2-cyclopentenone **1a**,  $\alpha$ -bromo-2-cyclohexenone **1b**, and  $\alpha$ -bromo-but-3-en-2-one **1c**, and several primary aliphatic amines were subjected to aziridination reaction in the presence of catalyst **II**. Aromatic amines (**2h–j**) and carbamates (**2k–l**) were found unreactive towards **1a**. Therefore, we herein report the catalytic potential of **II** in the synthesis of several bicyclic- $\alpha$ -ketoaziridines (**3**, **4**, and **5**).

The yields obtained in the reaction of **1a–c** with several nucleophiles are summarized in Table 1 and Scheme 5.

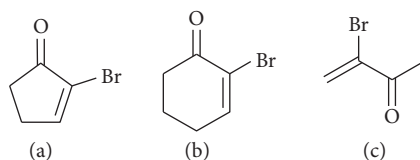


FIGURE 1: Michael acceptors.

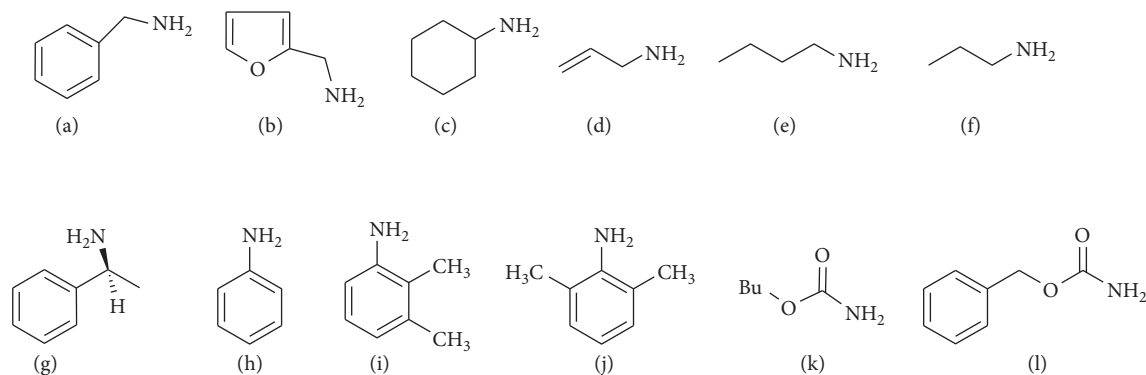
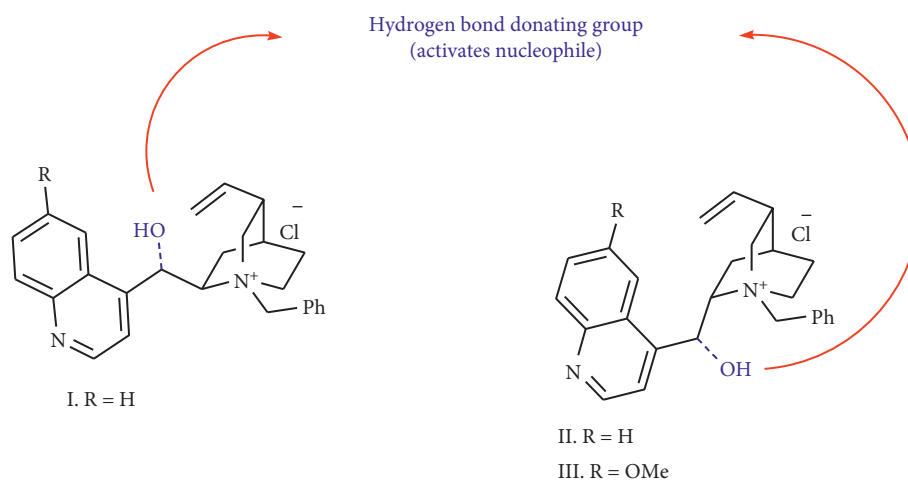


FIGURE 2: Michael donors.

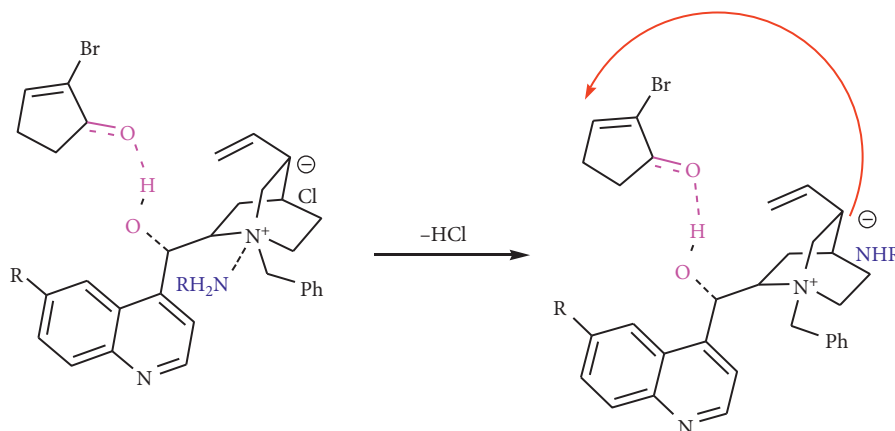
FIGURE 3: *Cinchona* alkaloid chloride PT catalysts tested.

For a phase-transfer catalytic reaction, the rate is usually determined by four steps: the aqueous phase reaction, organic phase reaction, mass transfer of species  $Q^+RNH^-$  from the aqueous phase to the organic phase, and mass transfer of species of the regenerated catalyst,  $Q^+Cl^-$ , from the organic phase back to the aqueous phase. The first and last two steps are fast processes. Therefore, the organic phase reaction, which is usually slow, is the rate determining step (Scheme 6) [14, 17]. However, factors that affect reaction rate are much more complex [17, 18].

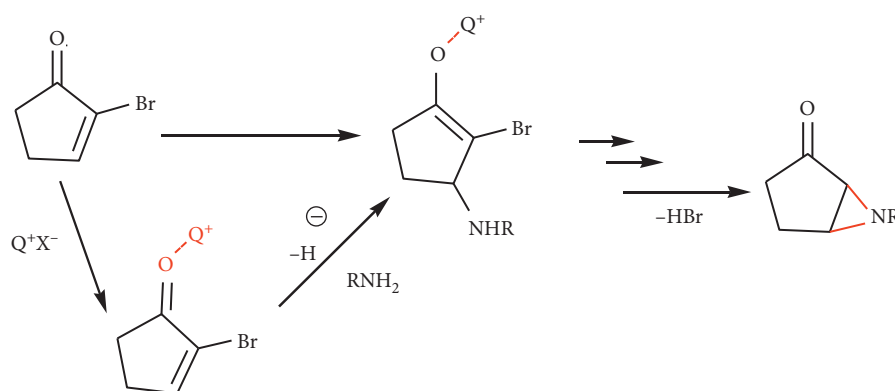
In principle, the catalytic efficiency increases with increases of the catalyst organophilicity. Accessibility of the catalyst (open-faced structure of  $Q^+$ ) and catalyst cross-sectional area are strongly correlated with reaction rate. The N-atom of the  $Q^+$  is considered less accessible as the chains

of the quaternary ammonium cation are bigger (soft ion) and the positive charge on the  $Q^+$  can be electrostatically interact weakly with the nucleophile (nucleophilic activation) [18, 19].

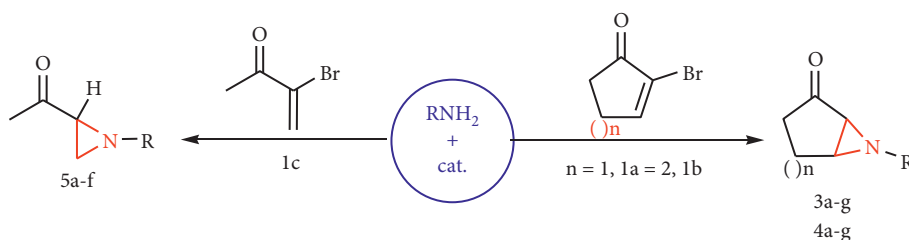
Therefore, cinchoninium cation- $Q^+$  having sufficient organic structure will permit the catalyst, and the anions easily partitioned into the organic phase. This increases the displacement rate and provides good partition coefficient between the phases. In this case, the nucleophile is suitably travelled from the interface to the organic phase. As a result, the organophilic catalyst displays a lower concentration in the aqueous phase (very little solvation), and activation energy significantly reduces. This increases the nucleophilicity of nucleophiles. Therefore, weak interaction that exists between the ion pair is a crucial factor for enhanced



SCHEME 3: Activation through hydrogen bonding.



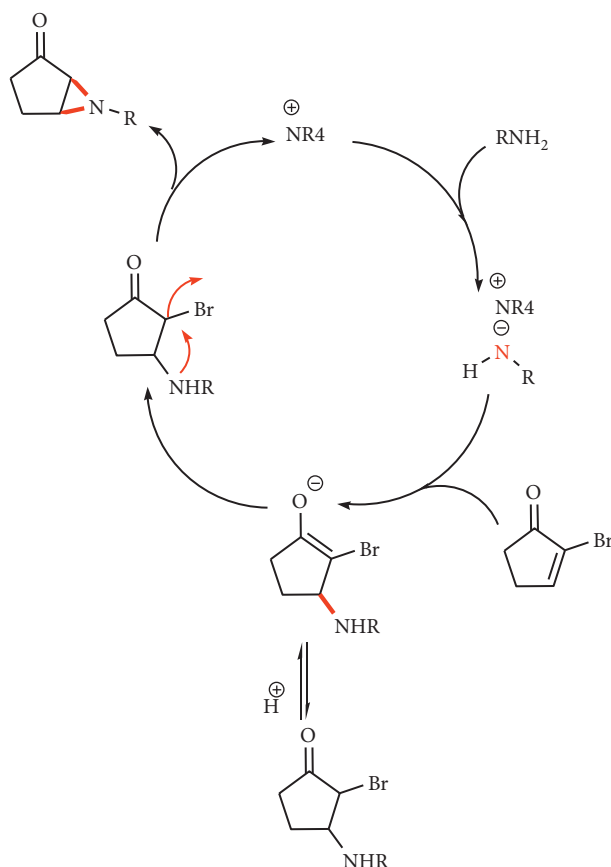
SCHEME 4: Activation through Lewis acid coordination.

SCHEME 5: The synthesis bicyclic- $\alpha$ -ketoaziridine.

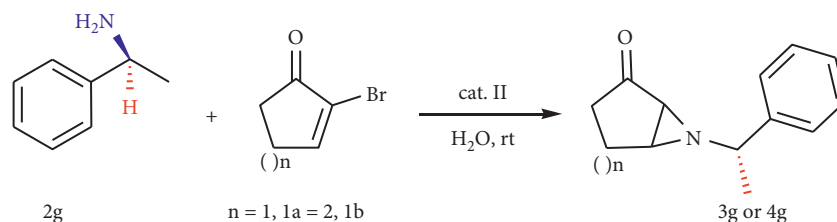
reactivity of salts of *Cinchona* alkaloids [17]. At the end of the reaction, an anionic leaving group is usually regenerated, and the catalyst then returns from organic phase to the aqueous phase to continue the cycle (Scheme 6).

A relatively less studied system is the nucleophilic addition of an anion lacking a prochiral center to prochiral electrophiles. When a chiral catalyst is used, the anion is expected to transfer into the organic phase as a chiral ion pair by ion-exchange with the catalyst. Then, it attacks mostly a prochiral electrophile to create a new stereogenic center [14]. The asymmetric conjugate addition of  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones using an aqueous solution of primary amine represents a typical example. The

chiral cinchoninium cation-anion ( $Q^+RHN^-$ ) is responsible for the enantiofacial discrimination of the prochiral enone. The pH value of the reaction is nearly neutral, so the possibility of side reactions is considerably reduced. However, it was observed that the catalysts were not enantioselective, and racemic products were isolated. Thus, a more accurate catalyst design would be required for the chiral cation ( $Q^+$ ) to recognize the enantiotopic faces of the electrophilic reacting partner. The selectivity, among others, is most commonly influenced by the complexation of the enone with 9-OH group of a cation. Notwithstanding, under this reaction conditions, it is proved that a bulky ammonium cation,  $Q^+$ , should weakly or not



SCHEME 6: Proposed mechanism of PT-catalyzed aziridination of  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -cyclopent-2-enone.



SCHEME 7: The synthesis of optically active ketoaziridines.

complexed with the enone; rather, it coordinates and transfer the nucleophile to the organic phase. Furthermore, equilibration is often possible, which favors the formation of the nonselective and thermodynamically favored 1, 4-adduct.

Optically active aziridines represent an extremely important building block in organic synthesis [4, 20, 21]. For these reasons and numerous others, we investigated the reaction between the chiral molecule, (*S*)-(-)-phenylethyl amine **2g**, and the Michael acceptors, **1a** and **1b**, to get optically active products (Scheme 7). **2g** reacts with **1a** to provide two readily separable diastereomers **A** and **B** (1 : 1) in 82% yield (Table 1, **3g**, entry 7). This amine also reacted smoothly with **1b** to furnish a 2 : 1 mixture of **C** and **D** diastereomers in 87% yield (Table 1, **4g**, entry 7). In this reaction, **1b** showed better diastereoselectivity possibly due to

its fixed conformation that gives relatively stable intermediate after conjugate addition.

Comparison among amines, for the reaction with  $\alpha$ -bromo- $\alpha$ ,  $\beta$ -unsaturated ketones, indicated that aromatic amines and carbamates are unreactive. This is probably due to low solubility and weak nucleophilicity of aromatic amines and carbamates compared with aliphatic amines. Accordingly, the formation of active anionic intermediate (the negative charge concentration on N-atom next to the phenyl ring) is not favorable for conjugate addition. The same is true for carbamates in which the negative charge on N-atom delocalizes into the carbonyl group and is not available for nucleophilic addition reaction. Therefore, the availability of the anionic intermediate is the crucial factor that determines the efficiency of this synthetic protocol for nucleophilic reaction.



## 4. Conclusion

Salts of *Cinchona* alkaloid catalyzed reaction could be used as an alternative approach for the synthesis of bicyclic- $\alpha$ -ketoaziridine. The scope of the protocol in terms of substrate and PT catalysts has been checked. According to this system, the efficiency of the procedure depends only on the purity and stoichiometry of the reactants. High yields, short reaction time, use of milder reaction conditions, easy workup, and operational simplicity are some of the advantages of this procedure. In comparison with other procedures, it allows the use of cheaper and non-toxic raw materials (for instance, water as a solvent and metal-free reaction) with environmentally friendly conditions.

## Abbreviations

CAIRC: Conjugate addition-initiated ring-closure  
PTC: Phase transfer  
TBAB: Tetrabutylammonium bromide  
TBAC: Tetrabutylammonium chloride  
Q<sup>+</sup>: Quaternary ammonium cation (cinchoninium cation)  
GLC: Gas liquid chromatography.

## Data Availability

All data generated or analyzed during this study are included in this published article.

## Disclosure

The contents of this manuscript have not been copyrighted or published previously, are not now under consideration for publication elsewhere, and will not be copyrighted, submitted, or published elsewhere, while acceptance by the journal is under consideration.

## Conflicts of Interest

The authors declare no conflicts of interest.

## Authors' Contributions

Alemayehu Mekonnen and Alemu Tesfaye conceived and designed the experiments. Alemayehu Mekonnen analyzed data and wrote the paper. Alemayehu Mekonnen performed the experiments. All authors participated in the revision of the manuscript.

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