Intramolecular Cyclization of Alkenyl Substrates Using Oxidative Umpolung of Alkali Metal Bromides by Inorganic Oxidants

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1. Oxidative Intramolecular Bromo-Amination of \( N \)-Alkenyl Sulfonamides via Umpolung of Alkali Metal Bromides.

Introduction

Intramolecular halo-cyclization\(^1\) is an important tool for the synthesis of nitrogen- or oxygen-containing heterocycles, which are useful building blocks of biologically active natural products and pharmacological products.\(^2\) In particular, some bromo compounds have been also noted in the biosynthesis of halogenated marine natural products\(^3\) and medicinal plants.\(^3a,4\) As for the bromo-amination of alkenes by both intermolecular and intramolecular reactions with \( N \)-protected amines, straightforward methods using transition metal catalysts and stoichiometric amounts of brominating reagents have been developed. However, those methods present a disadvantage in that toxic heavy metals (Os,\(^5\) Mn,\(^6\) V,\(^6\) Cu,\(^6,7\) or Pd\(^7,8\)) are required. On the other hand, such organic brominating reagents as \( N \)-bromosuccinimide (NBS),\(^9\) 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH),\(^10\) 2,4,4,6-tetrabromocyclohexa-2,5-dieneone (TBCO),\(^11\) and bromodiethylsulfonium bromopentachloroantimonate (BDSB)\(^12\) have been used as active bromo sources for chemo-selective bromo-cyclization reactions. However, they present a particular problem in that the stoichiometric amount of the corresponding organic waste is increased (Scheme 1, eq. 1). To overcome this problem, it is very important to develop a bromo cyclization using non-organic bromo reagents under heavy-metal-free conditions. Therefore, we focused on the oxidative bromo-cyclization via umpolung of alkali metal bromides, which can oxidize bromide ion (Br\(^-\)) (inorganic bromide) to activated bromonium-like species (Br\(^+\)) using various kinds of oxidants (Scheme 1, eq. 2).\(^13\)

![Scheme 1. Intramolecular Bromocyclization of Alkenes](image-url)
The oxidative umpolung reaction of bromide anion is related closely to the biosynthesis of vanadium bromoperoxydase (V-BrPO), which is used to synthesize halogenated organic compounds in seaweeds and marine algae. The V-BrPO catalyze the oxidation of a bromide anions (Br⁻) by hydrogen peroxide to produce the corresponding bromonium ion intermediate (Br⁺ or its equivalent) through two-electron oxidation. Continuously, the oxidized intermediate can halogenate an appropriate organic substrates, or react with another equivalent of hydrogen peroxide to form singlet oxygen (Scheme 2). In recent years, these oxidative bromination with vanadium catalyst has been reported.

In the past, the exo-selective intramolecular bromo-amination was developed. However, the reaction required NBS as the bromo reagent. The author report here an exo-selective intramolecular bromo-amination of N-alkenyl sulfonamides and N-alkenoxyl sulfonamides via umpolung of inorganic bromides.

Scheme 2. A Mechanism of Vanadium Bromoperoxydases (V-BrPO)

In the past, the exo-selective intramolecular bromo-amination was developed. However, the reaction required NBS as the bromo reagent. The author report here an exo-selective intramolecular bromo-amination of N-alkenyl sulfonamides and N-alkenoxyl sulfonamides via umpolung of inorganic bromides.
Results and Discussion.

First, the author screened a series of bromo reagents and oxidants for the intramolecular bromo-amination with 1a (Table 1). The use of Br₂ as bromo reagent for intramolecular bromo-amination was not suitable to give 2a in moderate yield together with many by-products (entry 1). In contrast, the use of NBS gave 2a in 90% yield (entry 2). When 1a was treated with KBr as the bromo reagent with m-CPBA or Oxone® as the oxidant in CH₂Cl₂, 2a was obtained in low yields (entries 3 and 4). Then, solvent effects on the intramolecular bromo-amination using KBr/Oxone® were investigated (entries 5-7). Whereas the treatment of 1a in THF and AcOEt gave 2a in 70% and 92% yields, respectively (entries 5 and 6), the reaction in MeCN gave 2a in >99% yield as the best result (entry 7). Use of other oxidants, such as m-CPBA, H₂O₂, PhI(OAc)₂, or t-BuOCl, in this reaction with 1a decreased the yield of 2a (entries 8-11). Furthermore, use of NaBr instead of KBr also decreased the yield of 2a (entry 12) and the use of KBr alone was totally ineffective for the transformation of 1a into 2a (entry 13).

Next, the author investigated the scope of the intramolecular bromo-amination of N-alkenyl sulfonamides 1 via the umpolung reaction of KBr under optimized reaction conditions (Table 2). The reaction of N-alkenyl sulfonamides bearing other sulfonyl groups, such as benzenesulfonyl (1b), 1-naphthalenesulfonyl (1c),
4-fluorobenzenesulfonyl (1d), n-butanesulfonyl (1e), and (1S)-camphorsulfonyl (1f), also gave the corresponding products in excellent yields (Table 2, entries 1-5). A variety of substituted alkenes underwent the intramolecular bromo-amination to give the corresponding aminobromides. When N-(2,2-dialkyl)substituted and N-(1,2-dialkyl) substituted 4-penten-1-yl sulfonamides 1g, 1h, 1i, and 1j were used, cyclization products 2g, 2h, 2i, and 2j were obtained in >99%, 97%, >99%, and 96% yields, respectively (entries 6-9). N-Alkenyl sulfonamides with cyclic alkenes 1k and internal alkenes (E)-1l and (Z)-1m were efficiently converted into corresponding products 2k, 2l, and 2m in high yields (89–91%) with good diastereoselectivities (dr = 77:23–>99:<1) (entries 10-12). Disubstituted terminal alkene 1n could be also used and corresponding product 2n with a quaternary carbon center was obtained in 90% yield (entry 13). Moreover, the same treatment of the chiral N-alkenyl sulfonamides (1o and 1p) derived from α-amino acids also provided corresponding products 2o and 2p in excellent yields with moderate diastereoselectivities (>99% and 93% yields, dr = 77:23 and 57:43), respectively (entries 14 and 15). Once the optimized conditions were established, other substrates were examined, and the scope of the intramolecular bromo-amination for several N-alkenyl sulfonimides is shown in Table 2 and Table 3.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield of 2 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>R = Ph (1b)</td>
<td>2b</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R = 1-Naphthyl (1c)</td>
<td>2c</td>
<td>16</td>
<td>93</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R = 4-F-C₆H₄ (1d)</td>
<td>2d</td>
<td>17</td>
<td>93</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R = n-Bu (1e)</td>
<td>2e</td>
<td>12</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>R = 1f</td>
<td>2f</td>
<td>3</td>
<td>98 (dr = 64:36)</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1g</td>
<td>2g</td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1h</td>
<td>2h</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>8&lt;sup&gt;f&lt;/sup&gt;</td>
<td>cis-1i</td>
<td>2i</td>
<td>8</td>
<td>&gt;99 (dr = 68:32)</td>
</tr>
<tr>
<td>9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>trans-1j</td>
<td>2j</td>
<td>5</td>
<td>98 (dr = 84:16)</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1k</td>
<td>2k</td>
<td>8</td>
<td>91 (dr = &gt;99:&lt;1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield.  
<sup>b</sup>Reaction was carried out in MeCN (2 ml).  
<sup>c</sup>Reaction was carried out under dark conditions.
The present method for the oxidative intramolecular bromo-amination of N-alkenyl sulfonamides was applied to the synthesis of bromo isoxazolidines from N-alkenoxy sulfonamide derivatives. Isoxazolidines are useful for the synthesis of biologically active compounds.\(^1\) They also serve as precursors to \(\gamma\)-amino alcohols,\(^1\) \(\gamma\)-amino ketones,\(^1\) \(\beta\)-amino acids,\(^1\) and 3-isoxazolidines.\(^1\) Isoxazolidines have been synthesized via the 1,3-dipolar cycloaddition reaction of nitrones with alkenes\(^1\) and the Pd-catalyzed cyclization of N- or O-homoallylic hydroxylamines.\(^2\) To the best of his knowledge, however, there has been no report of the synthesis for bromo isoxazolidines. The author reports here the first synthesis of bromo isoxazolidines via the oxidative intramolecular bromo-amination of N-alkenoxy sulfonamide derivatives \(3\) (Table 3). Treatment of \(3a\) \((R_1 = R_2 = R_3 = H)\) with KBr and Oxone\(^*\) in a 4:1 mixture of MeCN and toluene gave \(4a\) in 93% yield. The same treatment of 2-aryl substituted N-alkenoxy sulfonamides bearing H, MeO, and CF\(_3\) at aryl group \(3b, 3c,\) and \(3d\) \((R_1 = Ph, 4\text{-MeO-C}_6\text{H}_4,\) and \(4\text{-CF}_3\text{-C}_6\text{H}_4, R_2 = R_3 = H)\) also provided corresponding products \(4b, 4c,\) and \(4d\) in excellent yields (90–97%) with moderate diastereoselectivities \((\text{dr} = 4:1)\). Use of disubstituted internal alkene \(3e\) \((R_1 = 1\text{-naphthyl, } R_2 = \text{Me, } R_3 = H)\) and terminal alkene \(3f\) \((R_1 = 4\text{-Cl-C}_6\text{H}_4, R_2 = H, R_3 = \text{Me})\) provided corresponding products \(4e\) and \(4f\) in 91%
and 95% yields, respectively. Moreover, treatment of 2-thienyl substituted \(N\)-alkenoxyl sulfonamides 3g (\(R^1 = 2\)-thienyl, \(R^2 = R^3 = H\)) and 2-butyl substituted \(N\)-alkenoxyl sulfonamides 3h (\(R^1 = n\)-butyl, \(R^2 = R^3 = H\)) also gave desired products 4g and 4h in 82% and 98% yields, respectively.

![Chemical structure](image)

**Table 3.** Exo-selective Intramolecular Bromo-amination of Various \(N\)-alkenoxyl Sulfonamides (3).

<table>
<thead>
<tr>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a, 4h, 93%</td>
<td>(dr = 84:16)</td>
<td></td>
</tr>
<tr>
<td>4b, 4h 97%</td>
<td>(dr = 90:10)</td>
<td></td>
</tr>
<tr>
<td>4c, 10h, 50%</td>
<td>(dr = 90:10)</td>
<td></td>
</tr>
<tr>
<td>4d, 20h, 91%</td>
<td>(dr = 83:17)</td>
<td></td>
</tr>
<tr>
<td>4e, 18h, 92%</td>
<td>(dr = 81:19)</td>
<td></td>
</tr>
<tr>
<td>4f, 8h, 98%</td>
<td>(dr = 82:18)</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction was carried out under dark conditions.

*Starting materials with a 2:1 mixture of E/Z isomers were used.

*Reaction was carried out in a mixture of MeCN and toluene (1:1) (1 mL).

Next, the author carried out three experiments in order to further illuminate the mechanistic picture (**Scheme 3**). First, the treatment of \(N\)-pentyltosylamide (5) with KBr and Oxone® in MeCN gave \(N\)-bromo-\(N\)-pentyltosylamide (6) in 88% yield (**Scheme 3, eq. 1**). Second, when a mixture of 5 and \(N\)-methyl-\(N\)-(4-penten-1-yl)tosylamide (7) was
treated with KBr and Oxone in MeCN, only 7 was converted into some of unknown products (Scheme 3, eq. 2). In contrast, a mixture of 6 and 7 in MeCN were less converted than the reaction in eq. 3 (27% consumption of 7).

The proposed reaction mechanism is depicted in Scheme 4. The key step is the generation of the activated bromonium-like species (Br⁺), but not Br₂, via oxidative umpolung of KBr with Oxone® in MeCN at room temperature (Table 1, entries 1 vs 7). The author speculates that there are two pathways for the bromo-amination of N-alkenyl sulfonamides 1 with Br⁺. First, the reaction may occur via intermolecular bromination of the olefin moiety and then, the bromonium cation intermediate may be intramolecularly attacked by the sulfonamide group to form cyclization products 2 (path A). Alternatively, sulfonamides may undergo direct bromination to form N-bromo sulfonamides, followed by intramolecular bromonium ion transfer to the olefin moiety, and the cyclization of bromonium cation intermediate proceeds to afford desired products 2 (path B). Some of the mechanistic approaches to the intramolecular bromo-amination indicate that the activated bromonium-like species first brominate the olefin moiety of the substrates (path A).
In conclusion, the author has developed an oxidative intramolecular cyclizations using the unpolung of alkali metal bromide with Oxone®. These reactions provides the desired products without generating the stoichiometric amount of the corresponding organic wastes, thus contributing to green sustainable chemistry. And, these reactions proceeded to generate the $N$-containing heterocycles in high yields.
Experimental Section

$^1$H NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. $^{13}$C NMR spectra were measured on a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were performed by orbitrap mass spectrometers. Characteristic peaks in the Infrared (IR) spectra are recorded in wave numbers, cm$^{-1}$. Melting points are reported as uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica-gel plate (60F-254). The products were purified by column chromatography on silica gel 60 (63–200 mesh).

General Procedure for the Intramolecular Bromo-amination of N-Alkenyl Sulfonamides with a Metal Bromide / Oxone System (Table 1, entry 7). To a solution of 1a (59.8 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7 mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 3 h. Saturated NaHCO$_3$ aqueous solution (10mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL x 3). The combined extracts were washed by brine (10 mL) and dried over Na$_2$SO$_4$. The organic phase was concentrated under reduced pressure and the crude product was purified by silica-gel column chromatography (eluent: hexane/AcOEt = 5/1), to give the desired product 2a (79.2 mg, >99% yield).

2-(Bromomethyl)-1-tosylpyrrolidine (2a): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.51-1.61 (m, 1H), 1.69-1.80 (m, 1H), 1.81-1.89 (m, 1H), 1.90-1.98 (m, 1H), 2.44 (s, 3H), 3.15 (dt, $J$ = 10.1, 7.1 Hz, 1H), 3.36 (t, $J$ = 9.7 Hz, 1H), 3.51-3.44 (m, 1H), 3.74-3.79 (m, 1H), 7.34 (d, $J$ = 8.2 Hz, 2H), 7.73 (d, $J$ = 8.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 23.7, 30.2, 36.0, 49.8, 60.3, 127.5 (2C), 129.8 (2C), 134.0, 143.8. IR (neat) 1338, 1161, 1091, 1034, 986 cm$^{-1}$. MS (ESI) calcd for C$_{12}$H$_{17}$BrNO$_2$S [M + H]$^+$ 318.0158, found 318.0151. Anal. calcd for C$_{12}$H$_{16}$BrNO$_2$S: C, 45.29; H, 5.07; N, 4.40%. Found: C, 45.60; H, 5.16; N, 4.27%.

2-(Bromomethyl)-1-(phenylsulfonyl)pyrrolidine (2b): yield 95%, 72.2mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.51-1.61 (m, 1H), 1.68-1.80 (m, 1H), 1.80-1.90 (m, 1H), 1.91-2.00 (m, 1H), 3.17 (dt, $J$ = 10.1, 7.5Hz, 1H), 3.37 (t, $J$ = 9.8 Hz, 1H), 3.46-3.53 (m, 1H), 3.78 (dd, $J$
1H NMR (400 MHz, CDCl3) δ 1.63-1.73 (m, 1H), 1.82-1.92 (m, 2H), 1.93-2.04 (m, 1H), 3.36 (t, J = 9.7 Hz, 1H), 3.30-3.43 (m, 2H), 3.68 (dd, J = 10.1, 3.2 Hz, 1H), 4.12-4.20 (m, 1H), 7.52-7.64 (m, 2H), 7.64-7.71 (m, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.86 (d, J = 8.7 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ 24.0, 30.4, 35.6, 49.5, 59.7, 124.2, 125.1, 126.9, 128.2, 128.9, 129.0, 130.0, 133.5, 134.3, 134.6. IR (neat) 1347, 1159, 1133, 1029, 989 cm−1. MS (ESI) calcd for C15H17BrNO2S [M+H]+ 354.0158, found 354.0152.

2-(Bromomethyl)-1-(butylsulfonyl)pyrrolidine (2e): yield >99%, 71.1 mg. 1H NMR (400 MHz, CDCl3) δ 0.96 (t, J = 7.5 Hz, 3H), 1.47 (sext, J = 7.5Hz, 2H), 1.75-2.18 (m, 6H), 2.95-3.02 (m, 2H), 3.35-3.48 (m, 3H), 3.64 (dd, J = 10.3, 3.2 Hz, 1H), 4.04-4.12 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 13.6, 21.7, 24.6, 25.2, 30.4, 36.2, 49.4, 50.2, 59.7. IR (KBr) 1334, 1142, 1067, 1035, 989 cm−1. MS (ESI) calcd for C9H18BrNNaO2S [M+Na]+ 306.0134, found 306.0133.

2-(Bromomethyl)-1-[(1S)-10-camphorsulfonyl]pyrrolidine (2f, Diastereomeric Mixture): yield 98%, 92.7 mg. Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.90 (s, 3H), 1.14 (s, 3H), 1.39-1.48 (m, 1H), 1.62-1.71 (m, 1H), 1.88-2.22 (m, 7H), 2.34-2.45 (m, 1H), 2.47-2.58 (m, 1H), 2.88 (d, J = 14.9 Hz, 1H), 3.33-3.43 (m, 2H), 3.43-3.54 (m, 2H), 3.67 (dd, J = 10.3, 3.3Hz, 1H), 4.02-4.11 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 19.8, 20.0, 24.3, 25.2, 26.9, 30.4, 36.1, 42.6, 42.8, 45.8, 47.9, 49.4, 58.3, 60.1, 215.5.
Minor-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.90 (s, 3H), 1.15 (s, 3H), 1.39-1.48 (m, 1H), 1.62-1.71 (m, 1H), 1.88-2.22 (m, 7H), 2.34-2.45 (m, 1H), 2.47-2.58 (m, 1H), 2.84 (d, $J = 14.6$ Hz, 1H), 3.33-3.43 (m, 2H), 3.43-3.54 (m, 2H), 3.70 (dd, $J = 10.1$, 3.2 Hz, 1H), 3.99-4.08 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 19.8, 20.0, 24.2, 25.1, 26.9, 30.5, 35.9, 42.6, 42.8, 45.1, 47.9, 49.6, 58.2, 60.1, 215.3. IR (KBr) 1745, 1341, 1200, 1146, 1037 cm$^{-1}$. MS (ESI) calcd for C$_{15}$H$_{24}$BrNNaO$_3$S $[M + Na]^+$ 400.0552, found 400.0550.

2-(Bromomethyl)-4,4-dimethyl-1-tosylpyrrolidine (2g): yield >99%, 86.5 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.53 (s, 3H), 1.05 (s, 3H), 1.70 (dd, $J = 13.0$, 8.5 Hz, 1H), 1.88 (dd, $J = 13.0$, 7.6 Hz, 1H), 2.44 (s, 3H), 3.14 (d, $J = 10.8$ Hz, 1H), 3.19 (d, $J = 10.8$ Hz, 1H), 3.52 (t, $J = 9.6$ Hz, 1H), 3.82-3.91 (m, 1H), 3.94 (dd, $J = 9.6$, 3.0 Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.74 (d, $J = 7.8$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 25.7, 37.4, 37.5, 45.8, 60.0, 61.8, 127.5 (2C), 129.7 (2C), 134.8, 143.7. IR (KBr) 1345, 1157, 1092, 1043, 1024 cm$^{-1}$. MS (ESI) calcd for C$_{14}$H$_{21}$BrNO$_2$S $[M + H]^+$ 346.0471, found 346.0463.

3-(Bromomethyl)-2-tosyl-2-azaspiro[4.5]decane (2h): yield 97%, 93.7 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.59-0.69 (m, 1H), 0.74-0.84 (m, 1H), 1.05-1.50 (m, 8H), 1.63 (dd, $J = 13.3$, 8.5 Hz, 1H), 1.95 (dd, $J = 13.3$, 7.5 Hz, 1H), 2.43 (s, 3H), 3.15 (d, $J = 11.0$ Hz, 1H), 3.35 (d, $J = 11.0$ Hz, 1H), 3.50 (dd, $J = 9.8$, 9.0 Hz, 1H), 3.75-3.84 (m, 1H), 3.94 (dd, $J = 9.8$, 3.0 Hz, 1H), 7.33 (d, $J = 8.6$ Hz, 2H), 7.74 (d, $J = 8.6$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 22.7, 23.6, 25.7, 33.9, 36.1, 37.7, 41.4, 44.0, 59.0, 59.2, 127.4 (2C), 129.7 (2C), 134.6, 143.7. IR (KBr) 1350, 1220, 1160, 1090, 1031 cm$^{-1}$. MS (ESI) calcd for C$_{17}$H$_{25}$BrNO$_2$S $[M + H]^+$ 386.0784, found 386.0776. Anal. calcd for C$_{17}$H$_{24}$BrNO$_2$S: C, 52.85; H, 6.26; N, 3.63%. Found: C, 52.81; H, 6.27; N, 3.55%.

cis-2-(Bromomethyl)-1-tosloyctahydro-1H-indole (2i, Diastereomeric Mixture): yield >99%, 93.0 mg. Major-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.99-1.31 (m, 2H), 1.32-1.48 (m, 2H), 1.48-1.74 (m, 4H), 1.80-2.04 (m, 2H), 2.07-2.18 (m, 1H), 2.44 (s, 3H), 3.41 (t, $J = 9.8$ Hz, 1H), 3.62-3.71 (m, 1H), 3.71-3.78 (m, 1H), 4.00 (dd, $J = 9.8$, 3.6 Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 20.1, 21.6, 24.3, 25.7, 31.1, 34.1, 36.2, 37.8, 60.7, 61.4, 127.4 (2C), 129.8 (2C), 134.7, 143.6. Minor-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.85-0.99 (m, 1H), 0.99-1.31 (m, 2H), 1.32-1.48 (m, 2H), 1.48-1.74 (m, 4H), 1.80-2.04 (m, 2H), 2.43 (s, 3H), 3.28 (t, $J = 10.8$ Hz, 1H), 3.82-3.89 (m, 1H), 3.92-4.02 (m, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR(100 MHz, CDCl$_3$) $\delta$ 20.0, 21.5, 23.5, 25.6, 27.9, 31.6, 34.5, 35.5,
trans-2-(Bromomethyl)-1-tosyloctahydro-1H-indole (2j, Diastereomeric Mixture): yield 96%, 89.4 mg. Major diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.98-1.48 (m, 6H), 1.55-1.73 (m, 1H), 1.73-1.88 (m, 2H), 2.25-2.34 (m, 2H), 2.43 (s, 3H), 2.90 (dt, $J = 10.8, 3.2$ Hz, 1H), 3.60 (dd, $J = 9.8, 8.2$ Hz, 1H), 3.88 (dd, $J = 9.8, 3.2$ Hz, 1H), 4.27 (dq, $J = 8.2, 3.2$ Hz, 1H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 25.0 (2C), 29.3, 29.6, 36.4, 38.4, 45.3, 60.2, 66.3, 127.0 (2C), 129.6 (2C), 139.6, 143.0. Minor diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.98-1.48 (m, 6H), 1.55-1.88 (m, 3H), 1.99 (dd, $J = 12.6, 5.5$ Hz, 1H), 2.25-2.34 (m, 1H), 2.46 (s, 3H), 2.46-2.51 (m, 1H), 3.29 (dd, $J = 11.4, 10.6$ Hz, 1H), 3.76-3.84 (m, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.6, 24.5, 25.2, 29.4, 32.4, 33.1, 35.8, 42.7, 61.3, 67.3, 127.8 (2C), 129.7 (2C), 133.0, 143.8. IR (KBr) 1333, 1148, 1118, 1088, 1053 cm$^{-1}$. MS (ESI) calcd for C$_{16}$H$_{23}$BrNO$_2$S [M + Na]$^+$ 394.0447, found 394.0443.

cis-6-Bromo-1-tosyloctahydrocyclopenta[b]pyrrole (2k): yield 91%, 78.3 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.45-1.54 (m, 2H), 1.67-1.76 (m, 1H), 2.00-2.07 (m, 1H), 2.13-2.28 (m, 2H), 2.45 (s, 3H), 2.74-2.82 (m, 1H), 3.01 (td, $J = 10.1, 7.3$ Hz, 1H), 3.45 (td, $J = 10.1, 6.1$ Hz, 1H), 3.89 (d, $J = 7.6$ Hz, 1H), 4.77 (d, $J = 3.9$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.73 (d, $J = 8.5$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.6, 29.8, 30.7, 33.9, 41.9, 50.0, 57.6, 73.3, 127.9 (2C), 129.8 (2C), 132.8, 143.9. IR (KBr) 1345, 1157, 1094, 1026 cm$^{-1}$. MS (ESI) calcd for C$_{14}$H$_{18}$BrNaO$_2$S [M + Na]$^+$ 366.0134, found 366.0126. Anal calcd for C$_{14}$H$_{18}$BrNO$_2$S: C, 48.84; H, 5.27; N, 4.07%. Found: C, 48.96; H, 5.20; N, 4.02%.

syn-2-(1-Bromomethyl)-1-tosylpyrrolidine (2l): yield 89%, 73.9 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.40 (dt, $J = 12.1, 7.6$ Hz, 1H), 1.68 (d, $J = 7.1$ Hz, 1H), 1.68-1.80 (m, 1H), 1.82-1.92 (m, 1H), 1.95-2.03 (m, 1H), 2.43 (s, 3H), 3.34 (dd, $J = 7.6, 5.9$ Hz, 2H), 3.69 (dt, $J = 8.2, 4.7$ Hz, 1H), 4.61 (dq, $J = 7.1, 4.7$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.73 (d, $J = 8.2$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 23.1, 24.5, 27.9, 49.4, 55.1, 65.0, 127.5 (2C), 129.7 (2C), 135.1, 143.6. IR (KBr) 1343, 1156, 1092, 1044, 996 cm$^{-1}$. MS (ESI) calcd for C$_{13}$H$_{19}$BrNO$_2$S [M+ H]$^+$ 332.0314, found 332.0314.

anti-2-(1-Bromomethyl)-1-tosylpyrrolidine (2m): yield 90%, 74.8 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.37-1.49 (m, 1H), 1.66 (d, $J = 7.1$ Hz, 3H), 1.71-1.83 (m, 2H), 1.95-2.05 (m,
1H), 2.45 (s, 3H), 3.26 (dt, J = 10.7, 7.1 Hz, 1H), 3.47 (dt, J = 10.7, 6.2 Hz, 1H), 3.93 (dt, J = 8.0, 4.1 Hz, 1H), 4.68 (dq, J = 7.1, 4.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 18.6, 21.5, 24.5, 27.0, 50.8, 51.0, 64.1, 127.6 (2C), 129.8 (2C), 133.6, 143.8. IR (KBr) 1341, 1160, 1087, 1004, 978 cm$^{-1}$. MS (ESI) calcd for C$_{13}$H$_{19}$BrNO$_2$S [M + H]$^+$ 332.0314, found 332.0307.

2-(Bromomethyl)-2-methyl-1-tosylpyrrolidine (2n): yield 90%, 74.8 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.57 (s, 3H), 1.67-1.92 (m, 3H), 2.25-2.33 (m, 1H), 2.42 (s, 3H), 3.31-3.39 (m, 1H), 3.39-3.46 (m, 1H), 3.76 (d, J = 10.3 Hz, 1H), 3.86 (d, J = 10.3 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.5, 22.5, 24.0, 39.3, 41.0, 49.8, 67.3, 127.3 (2C), 129.5 (2C). IR (KBr) 1338, 1155, 1120, 1064, 1005 cm$^{-1}$. MS (ESI) calcd for C$_{13}$H$_{19}$BrNO$_2$S [M + H]$^+$ 332.0314, found 332.0309.

(5S)-2-(Bromomethyl)-5-methyl-1-tosylpyrrolidine (2o, Diastereomic Mixture): yield $>99\%$, 83.0 mg. Major-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.14 (d, J = 6.4 Hz, 3H), 1.50-1.57 (m, 2H), 2.07-2.12 (m, 2H), 2.43 (s, 3H), 3.23 (t, J = 10.1 Hz, 1H), 3.90 (dd, J = 9.8, 3.3 Hz, 1H), 4.02-4.16 (m, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 20.5, 21.6, 27.8, 30.9, 34.6, 57.4, 60.6, 127.1 (2C), 129.7 (2C), 138.9, 143.3. Minor-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.35 (d, J = 6.4 Hz, 3H), 1.58-1.74 (m, 2H), 2.02-2.20 (m, 2H), 2.44 (s, 3H), 3.33 (t, J = 6.4 Hz, 1H), 3.71 (q, J = 6.4 Hz, 1H), 3.80 (dd, J = 9.6, 3.2 Hz, 1H), 3.79-3.87 (m, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.6, 23.2, 28.9, 31.8, 36.4, 58.3, 62.1, 127.6 (2C), 129.9 (2C), 134.4, 143.8. IR (neat) 1340, 1157, 1095, 1040 cm$^{-1}$. MS (ESI) calcd for C$_{13}$H$_{18}$BrNNaO$_2$S [M + Na]$^+$ 354.0134, found 354.0125.

(5R)-2-(Bromomethyl)-5-isopropyl-1-tosylpyrrolidine (2p, Diastereomeric Mixture): yield 93%, 83.8 mg. Major-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.40 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H), 1.23-1.34 (m, 1H), 1.60-1.72 (m, 1H), 1.72-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.00-2.10 (m, 1H), 2.42 (s, 3H), 3.28 (t, J = 10.0 Hz, 1H), 3.85-3.89 (m, 1H), 4.03 (dd, J = 9.7, 2.2 Hz, 1H), 4.15-4.21 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 15.2, 19.8, 21.5, 22.9, 29.3, 31.2, 34.6, 61.9, 65.7, 126.8 (2C), 129.5 (2C), 138.9, 143.1. Minor-diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.91 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 1.60-1.72 (m, 1H), 1.72-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.00-2.10 (m, 1H), 2.30-2.41 (m, 1H), 2.44 (s, 3H), 3.25 (t, J = 11.2 Hz, 1H), 3.41-3.47 (m, 1H), 3.76-3.84 (m, 2H), 7.34 (d, J =
3-(Bromomethyl)-2-tosylisoxazolidine (4a): yield 93%, 74.7 mg. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.17-2.30 (m, 1H), 2.46 (s, 3H), 2.43-2.53 (m, 1H), 3.35 (t, $J$ = 9.7 Hz, 1H), 3.66 (dd, $J$ = 10.2, 4.9 Hz, 1H), 3.94-4.06 (m, 2H), 4.44-4.53 (m, 1H), 7.36 (d, $J$ = 8.0 Hz, 2H), 7.86 (d, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.7, 34.8, 42.5, 60.9, 83.7, 126.9 (2C), 128.7 (2C), 129.0, 129.3 (2C), 129.8 (2C), 132.5, 145.4. IR (KBr) 1358, 1172, 1087, 1027, 1006 cm$^{-1}$. MS (ESI) calcd for C$_{17}$H$_{18}$BrNO$_3$S [M + Na]$^+$ 418.0083, found 418.0071. Anal. calcd for C$_{17}$H$_{18}$BrNO$_3$S: C, 51.52; H, 4.58; N, 3.53%. Found: C, 51.66; H, 4.54; N, 3.36%.

3-(Bromomethyl)-5-phenoxy-2-tosylisoxazolidine (4c, Diastereomeric Mixture): yield 90%, 95.9 mg. Data are for the major diastereomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.22 (ddd, $J$ = 12.8, 10.2, 8.9 Hz, 1H), 2.46 (s, 3H), 2.43-2.53 (m, 1H), 3.24 (t, $J$ = 9.7 Hz, 1H), 3.52 (t, $J$ = 10.4 Hz, 1H), 3.78 (s, 3H), 3.79 (dd, $J$ = 10.4, 4.6 Hz, 1H), 4.57-4.68 (m, 1H), 5.06 (dd, $J$ = 10.8, 5.5 Hz, 1H), 6.86 (d, $J$ = 8.8 Hz, 2H), 7.22 (d, $J$ = 8.8 Hz, 2H), 7.35 (d, $J$ = 8.2 Hz, 2H), 7.88 (d, $J$ = 8.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.7, 34.9, 42.2, 55.3, 61.0, 83.5, 114.0 (2C), 127.4, 128.5 (2C), 129.3 (2C), 129.8 (2C), 132.5, 145.3, 160.2. IR (KBr) 1517, 1356, 1254, 1166, 1030 cm$^{-1}$. MS (ESI) calcd for C$_{18}$H$_{21}$BrNO$_4$S [M+H]$^+$ 426.0369, found 426.0356.
3-(1-Bromoethyl)-5-(naphthalen-1-yl)-2-tosylisoxazolidine (4e, Diastereomeric Mixture): yield 91%, 104.73 mg. Major diastereomer: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 0.66 (d, \( J = 7.3 \) Hz, 3H), 2.44 (s, 3H), 3.16-3.26 (m, 1H), 3.49 (dd, \( J = 11.4, 10.1 \) Hz, 1H), 3.96 (dd, \( J = 10.1, 4.5 \) Hz, 1H), 7.36 (d, \( J = 8.3 \) Hz, 2H), 7.40-7.53 (m, 4H), 7.56 (d, \( J = 7.3 \) Hz, 1H), 7.80 (d, \( J = 8.2 \) Hz, 1H), 7.87 (d, \( J = 8.4 \) Hz, 1H), 7.91 (d, \( J = 8.3 \) Hz, 2H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 8.2, 21.7, 29.8, 41.8, 65.5, 82.0, 121.9, 123.8, 125.1, 125.7, 126.3, 128.4, 129.0, 129.6 (3C), 129.8, 129.9 (2C), 131.3, 133.3, 145.5. Minor diastereomer: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.23 (d, \( J = 6.6 \) Hz, 3H), 2.43 (s, 3H), 2.88-2.99 (m, 1H), 3.73-3.88 (m, 2H), 4.32 (dt, \( J = 7.5, 4.1 \) Hz, 1H), 5.57 (d, \( J = 10.3 \) Hz, 1H), 7.33 (d, \( J = 8.0 \) Hz, 2H), 7.42-7.58 (m, 3H), 7.85 (t, \( J = 7.6 \) Hz, 2H), 7.93 (d, \( J = 8.4 \) Hz, 2H), 8.03 (d, \( J = 8.5 \) Hz, 1H), 8.11 (d, \( J = 8.5 \) Hz, 1H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 15.0, 21.7, 34.5, 48.1, 66.1, 85.9, 123.3, 125.1, 125.2, 125.9, 126.5, 128.8, 129.2 (2C), 129.8 (3C), 129.9, 131.9, 132.9, 133.8, 145.2. IR (neat) 1494, 1333, 1161, 1092 cm\(^{-1}\). MS (ESI) calcd for C\(_{22}\)H\(_{23}\)BrNO\(_3\)S [M + H]\(^+\) 460.0577, found 460.0563.

3-(Bromomethyl)-5-(4-chlorophenyl)-3-methyl-2-tosylisoxazolidine (4f, Diastereomeric Mixture): yield 95%, 105.6 mg. Data are for the major diastereomer: \( ^1H \) NMR(400 MHz, CDCl\(_3\)) \( \delta \) 1.99 (s, 3H), 2.43 (s, 3H), 2.63 (dq, \( J = 12.8, 7.3 \) Hz, 2H), 3.61 (d, \( J = 10.5 \) Hz, 1H), 3.74 (d, \( J = 10.5 \) Hz, 1H), 5.55 (t, \( J = 8.0 \) Hz, 1H), 7.21 (d, \( J = 8.6 \) Hz, 2H), 7.26-7.34 (m, 4H), 7.85 (d, \( J = 8.6 \) Hz, 2H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 21.7, 21.9, 41.4, 48.8, 70.8, 81.7, 128.0 (2C), 128.8 (4C), 129.5 (2C), 134.5, 135.1, 135.5, 144.8. IR (neat) 1494, 1333, 1161, 1092 cm\(^{-1}\). MS (ESI) calcd for C\(_{18}\)H\(_{20}\)BrClNO\(_3\)S [M + H]\(^+\) 444.0030, found 444.0018.

3-(Bromomethyl)-5-(thiophen-2-yl)-2-tosylisoxazolidine (4g, Diastereomeric Mixture): yield 82%, 82.5 mg. Data are for the major diastereomer: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.36 (ddd, \( J = 12.8, 9.8, 7.1 \) Hz, 1H), 2.45 (s, 3H), 2.97 (ddd, \( J = 12.8, 7.8, 6.3 \) Hz, 1H), 3.51 (t, \( J = 10.1 \) Hz, 1H), 3.77 (dd, \( J = 10.1, 4.9 \) Hz, 1H), 4.64-4.74 (m, 1H), 5.50 (dd, \( J =
9.8, 6.3 Hz, 1H), 6.97 (dd, J = 5.0, 3.6 Hz, 1H), 7.04-7.08 (m, 1H), 7.32 (dd, J = 5.0, 1.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.7, 34.5, 42.4, 60.9, 79.4, 126.8, 126.9, 127.5, 129.3 (2C), 129.8 (2C), 132.4, 138.3, 145.4. IR (KBr) 1354, 1326, 1169, 1092, 1032 cm⁻¹. MS (ESI) calcd for C15H17BrNO3S2 [M + H]+ 401.9828, found 401.9817.

3-(Bromomethyl)-5-butyl-2-tosylisoxazolidine (4h, Diastereomeric Mixture): yield 98%, 92.2 mg. Data are for the major diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.87 (t, J = 7.0 Hz, 3H), 1.16-1.37 (m, 4H), 1.41-1.69 (m, 2H), 1.79 (ddd, J = 12.5, 10.2, 7.8 Hz, 1H), 2.46 (s, 3H), 2.59 (ddd, J = 12.5, 7.8, 5.5 Hz, 1H), 3.38 (t, J = 9.7 Hz, 1H), 3.71 (dd, J = 10.2, 4.6 Hz, 1H), 3.98-4.07 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 13.8, 21.7, 22.4, 28.1, 32.2, 34.9, 40.4, 60.7, 82.4, 129.2 (2C), 129.8 (2C), 132.5, 145.2. IR (neat) 1454, 1360, 1167, 1091, 1017 cm⁻¹. MS (ESI) calcd for C15H23BrNO3S [M+H]+ 376.0577, found 376.0565.

Mechanistic Study for Oxidative Intramolecular Bromo-amination of N-Alkenyl Sulfonamides via Umpolung of Alkali Metal Bromides (Table 2). N-Bromination of N-pentenyltosylamide (5) via oxidative umpolung of KBr (eq 1): To a solution of 5 (60.3 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7 mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 15 h. Saturated NaHCO₃ aqueous solution (10 mL) was poured into the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na₂SO₄. The organic phase was concentrated under reduced pressure, and the residue was the pure desired product (6) (70.7 mg, 88% yield) without further purification.

NPentyltosylamide (5): 1H NMR (400 MHz, CDCl3) δ 0.83 (t, J = 6.9 Hz, 3H), 1.18-1.28 (m, 4H), 1.41-1.49 (m, 2H), 2.43 (s, 3H), 2.91 (q, J = 6.9 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 13.8, 21.5, 22.1, 28.6, 29.1, 43.1, 127.0 (2C), 129.6 (2C), 136.9, 143.3. IR (neat) 3281, 1425, 1325, 1160, 1094 cm⁻¹. MS (ESI) calcd for C12H20NO2S [M + H]+ 242.1209, found 242.1201.

NBromo-Npentyltosylamide (6): 1H NMR (400 MHz, CDCl3) δ 0.90 (t, J = 7.1 Hz, 3H), 1.28-1.37 (m, 4H), 1.58-1.68 (m, 2H), 2.47 (s, 3H), 3.14 (t, J = 7.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 13.9, 21.7, 22.1, 27.8,
General Procedure for the Competitive Bromination of N-Sulfonamides (eq 2): To a solution of 5 (60.3 mg, 0.25 mmol), 7 (63.3 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7 mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 15 h. Saturated NaHCO₃ aqueous solution (10 mL) was poured into the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na₂SO₄. The organic phase was concentrated under reduced pressure, and the residue was a mixture of products 5 (48.5 mg, 80% yield), 7 (1.4 mg, 2% yield), and unknown products, yield (%) of which was estimated by ¹H NMR analysis.

N-Methyl-N(4-penten-1-yl)tosylamide (7): ¹H NMR (400 MHz, CDCl₃) δ 1.58-1.68 (m, 2H), 2.06-2.14 (m, 2H), 2.43 (s, 3H), 2.71 (s, 3H), 2.99 (t, J = 7.3 Hz, 2H), 4.96-5.08 (m, 2H), 5.80 (ddt, J = 17.2, 10.4, 6.6 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 21.5, 26.8, 30.6, 34.7, 49.6, 115.3, 127.4 (2C), 129.6 (2C), 134.4, 137.5, 143.2. IR (neat) 1460, 1341, 1160, 1091 cm⁻¹. MS (ESI) calcd for C₁₃H₂₀NO₂S [M+H]+ 254.1209, found 254.1201.
References


2. Bronsted Acid-assisted Intramolecular Aminohydroxylation of N-Alkenylsulfonamides under Heavy Metal-free Conditions

Introduction

The aminooxygenation of olefins is a very important strategy to directly provide 1,2-aminoalcohol derivatives that serve as useful building blocks in the synthesis of drugs and natural products.\textsuperscript{1,2} In particular, the intramolecular aminooxygenation of N-protected alkenes furnishes nitrogen-containing heterocycles that possess a variety of biological activities.\textsuperscript{3} Previously, reported methods required the use of heavy metals, such as Os\textsuperscript{4}, Pd\textsuperscript{5}, Cu\textsuperscript{6}, and Au\textsuperscript{7}, for the intramolecular aminooxygenation of N-protected alkenes (Scheme 1, eq 1). Heavy metal-free reactions of N-protected amines with iodine reagents such as bis(trifluoroacetoxyiodo)benzene(I(III), PIFA)\textsuperscript{8}, NIS\textsuperscript{9}, iodosylbenzene\textsuperscript{10}, and chiral aryliodine diacetate(I(III))\textsuperscript{11} were developed as sustainable strategies. However, the reactions with N-alkenylamides produced a stoichiometric amount of organic waste derived from the organic oxidant. The author reports here a heavy metal-free intramolecular aminohydroxylation of N-alkenyl sulfonamides using a Bronsted acid-assisted inorganic oxidant, which is the simplest aminooxygenation method and produces no stoichiometric amount of organic waste (Scheme 1, eq 2).

\begin{center}
\textbf{Scheme 5. Intramolecular Aminooxygenation of N-Protected Alkenes}
\end{center}

Previous work

\begin{eqnarray}
\text{Os, Pd, Cu, and Au} & & \text{Organic oxidant} \\
\text{NH} & & \text{NH} \\
\text{GP} & & \text{PG} \\
\text{Os, Pd, Cu, and Au} & & \text{Organic oxidant} \\
\text{NH} & & \text{NH} \\
\text{GP} & & \text{PG}
\end{eqnarray}

(1)

This work

\begin{eqnarray}
\text{Brønsted acid} & & \text{Inorganic oxidant} \\
\text{\textquoteleft Non-heavy metal\textquoteright} & & \text{\textquoteleft Few organic waste\textquoteright} \\
\text{NH} & & \text{NH} \\
\text{GP} & & \text{PG} \\
\text{Brønsted acid} & & \text{Inorganic oxidant} \\
\text{NH} & & \text{NH} \\
\text{GP} & & \text{PG}
\end{eqnarray}

(2)
Results and Discussion

Initially, the author optimized the reaction conditions for the intramolecular aminohydroxylation of N-alkenyl sulfonamides (Table 5). When 8a was treated with Oxone® (2KHSO5·KHSO4·K2SO4) in a mixture of MeCN and H2O (1:1) at room temperature, 9a was obtained in 74% yield (entry 1). The addition of TsOH·H2O as Brønsted acid to activate the cyclization increased the yield of 9a (entry 2). The use of other Brønsted acids, such as PhCO2H, (PhO)2P(O)OH, and (CF3SO2)2NH, decreased the yield of 9a (entries 3–5). The use of MeNO2, AcOEt, and CH2Cl2 instead of MeCN as organic solvent was not effective as an organic solvent for the intramolecular aminohydroxylation (entries 6–8). Under basic conditions, the reaction with K2CO3 (1.5 equiv) became less effective, and increasing the amount of K2CO3 to 3.0 equiv had no effect whatsoever on the transformation of 8a into 9a (entry 9). Raising the reaction temperature to 50 °C furnished 9a in a quantitative yield (entry 10). The use of other oxidants and changing the ratio of MeCN to H2O as solvent at 50 °C had negligible effects compared to the use of Oxone® in a 1:1 mixture of MeCN and H2O (entries 11–16). Interestingly, the reaction in H2O produced a cyclization product in 81% yield (entry 13).

Table 5. Screening of Optimal Conditions for Intramolecular Aminohydroxylation of 8a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oxone</td>
<td></td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Oxone</td>
<td>PhCO2H</td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>Oxone</td>
<td>(PhO)2P(O)OH</td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>Oxone</td>
<td>(CF3SO2)2NH</td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>MeNO2:H2O(1:1), rt</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>AcOEt:H2O(1:1), rt</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>CH3Cl2:H2O(1:1), rt</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Oxone</td>
<td>K2CO3</td>
<td>MeCN:H2O(1:1), rt</td>
<td>24</td>
<td>44%(0) b</td>
</tr>
<tr>
<td>10</td>
<td>Oxone</td>
<td></td>
<td>MeCN:H2O(1:1), 50°C</td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>11</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:1), 50°C</td>
<td>10</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(2:1), 50°C</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>13</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:2), 50°C</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>14</td>
<td>Oxone</td>
<td>TsOH·H2O</td>
<td>H2O, 50°C</td>
<td>20</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>H2O2</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:1), 50°C</td>
<td>20</td>
<td>0</td>
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<tr>
<td>16</td>
<td>TBHP</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:1), 50°C</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>t-BuOCl</td>
<td>TsOH·H2O</td>
<td>MeCN:H2O(1:1), 50°C</td>
<td>10</td>
<td>84</td>
</tr>
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</table>

a Yield of 9a with K2CO3 (1.5 equiv), and 8a was recovered in 56% yield.

b Yield of 9a with K2CO3 (3.0 equiv), and 8a was recovered in 99% yield.
Then, the author investigated the scope of the heavy metal-free intramolecular aminohydroxylation of N-alkenyl sulfonamides 8 under the optimized reaction conditions (Table 5). The reaction of N-alkenyl sulfonamides bearing other sulfonyl groups, such as 4-fluorobenzenesulfonyl (8b), 4-nitrobenzenesulfonfyl (8c), \(\sigma\)-butanesulfonfyl (8d), and \((S)\)-camphorsulfonfyl (8e), gave corresponding products (9b–9e) in high yields (78–97%) (entries 1–4). When monoalkyl- and dialkyl-substituted alkenylsulfonamides (8f–8j) were treated with Oxone® (1.5 or 2.0 equiv), cyclization products (9f–9j) were obtained in excellent yields (91–98%) (entries 5–9). The reaction of N-sulfonyl-2-allylcyclohexylamines (8k and 8l) and N-sulfonyl-2-allylaniline (8m) with Oxone® (2.0 equiv) in a 2:1 mixture of MeCN and H₂O also provided hexahydroindoline derivatives (9k and 9l) and the indoline derivatives (9m) in high yields (78–90%), respectively (entries 10–12). \(\pi\)-Electron-rich disubstituted internal alkenes (8n and 8o) and disubstituted terminal alkene (8p) were efficiently converted into prolinol derivatives bearing a secondary alcohol group (9n and 9o) and a quaternary carbon center (9p), respectively, in high yields (78–91%) (entries 13–15). Moreover, N-alkenyl sulfonamide bearing a hydroxy group (8q) also provided 4-hydroxyprolinol derivative (9q) in 91% yield (entry 16). Unfortunately, the reaction of diastereotopic N-alkenyl sulfonamides gave moderate to low diastereoselectivities (dr = 77:23–54:46).
**Table 5. Intramolecular Aminohydroxylation of N-Alkenyl Sulfonamides (8).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield of 9 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = 4-F-C₆H₄ (8b)</td>
<td>9b</td>
<td>13</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>R = 4-NO₂-C₆H₄ (8c)</td>
<td>9c</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>R = 4-NO₂-C₆H₄ (8d)</td>
<td>9d</td>
<td>72</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>R = 8e</td>
<td>9e</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(dr = 55:45)</td>
</tr>
<tr>
<td>5</td>
<td>Me NH₅Ts 8f</td>
<td>9f</td>
<td>22</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(dr = 50:50)</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NH₅Ts 8g</td>
<td>9g</td>
<td>78</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(dr = 52:48)</td>
</tr>
<tr>
<td>7</td>
<td>NH₅Ts 8h</td>
<td>9h</td>
<td>72</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(dr = 54:46)</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NH₅Ts 8i</td>
<td>9i</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NH₅Ts 8j</td>
<td>9j</td>
<td>72</td>
<td>98</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction was carried out at room temperature.  
<sup>b</sup>Oxone (2.0 equiv.) was used.  
<sup>c</sup>Oxone (2.0 equiv) was used in a 2:1 mixture of MeCN and H₂O.  
<sup>d</sup>Reaction was carried out without TsOH-H₂O at 0 °C.
The catalytic Brønsted acid (TsOH or KSO₄H) activates Oxone® as an electrophilic oxidant to form activated peroxymonosulfate intermediate (A)¹² in situ. Intermediate (A) promotes the intramolecular aminohydroxylation of N-alkenylsulfonamides, particularly electron-poor mono-substituted olefins. This reaction proceeds through a tandem reaction via the epoxidation of olefins, followed by the exo-selective intramolecular amination of epoxides (Scheme 6).¹²,¹³
Once prolinol derivatives 9 are formed, they are readily transformed into N-sulfonyl proline derivatives 10 by the treatment with (diacetoxyiodo)benzene (DIB) (2.2 equiv.) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (10 mol%) in a 1:1 mixture of MeCN and H2O at room temperature (Table 6). The reactions of 9a, 9c, 9d, 9f, and 9g gave corresponding products 10a, 10c, 10d, 10f, and 10g in high yields (80–>99%), respectively.

Finally, the author investigated the possibility of synthesizing of proline ethyl ester 12a through the cleavage of the sulfonyl groups of N-sulfonylproline 11a under mild conditions (Scheme 7). Thus, 10a was treated with EtI and K2CO3 to obtain N-tosyl-protected proline ethyl ester 11a in a quantitative yield. Removal of the tosyl
group in 11a with phenol in aqueous HBr solution and AcOH\textsuperscript{15} provided desired proline ethyl ester 12a as a hydrogen bromide salt in 94% yield.

Scheme 7. Synthesis of Proline Ethyl Ester (12a) by Desulfonylation of N-Sulfonyl amide (11a).

In conclusion, the author has developed an intramolecular aminohydroxylation of N-alkenyl sulfonamides (8) that proceeds under heavy metal-free conditions. This reaction, which was promoted by a Brønsted acid catalyst, activated a peroxymonosulfate complex to obtain N-sulfonyl prolinol derivatives (9). Moreover, 9 were transformed into N-sulfonyl proline derivatives (10) by oxidation using a DIB/TEMPO system and 11 was, in turn, converted into proline ethyl ester (12) by desulfonylation under mild conditions.
**Experimental Section**

**General Procedure.**

$^1$H NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. $^{13}$C NMR spectra were measured on a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were performed by orbitrap mass spectrometers. Characteristic peaks in the Infrared (IR) spectra are recorded in wave numbers, cm$^{-1}$. Melting points are reported as uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plate (60F-254). The products were purified by column chromatography on silica gel 60 (63–200 mesh). Visualization was accomplished by UV light (254 nm), anisaldehyde, KMnO$_4$, and phosphomolybdic acid. N-Alkenyl sulfonamides 8a–8e, 8h–8j, and 8m–8p, 16a 8f and 8g, 16b 8k and 8l, 16c,d 8m, 16e and 8q$^{4g}$ were prepared according to the literature procedure. Spectroscopic data of 9a$^{6b}$, 9h$^{17a}$, 9i$^{6b}$, 9m$^{6b}$, 9q$^{4g}$, 10a$^{17b}$, and 11a$^{17c}$ were in accord with those reported in the literature.

**4-Fluoro-$N$-(pent-4-en-1-yl)phenylsulfonamide (8b):** Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.57 (quin, $J = 7.1$ Hz, 2H), 2.05 (q, $J = 6.8$ Hz, 2H), 2.96 (q, $J = 7.1$ Hz, 2H), 4.91 (brs, 1H), 4.92–5.00 (m, 2H), 5.70 (ddt, $J = 17.2, 10.5, 6.8$ Hz, 1H), 7.19 (d, $J = 8.8$ Hz, 2H), 7.90 (dd, $J = 8.8, 5.0$ Hz, 2H). $^{13}$C NMR(100 MHz, CDCl$_3$) $\delta$ 28.6, 30.5, 42.6, 52.3, 115.6, 137.2. IR (neat) 3289, 2962, 1432, 1322, 1144, 1082 cm$^{-1}$. MS (ESI) calcd for C$_{11}$H$_{15}$FNO$_2$S [M + H]$^+$ 244.0802, found 244.0801.

**$N$-(Pent-4-en-1-yl)butan-1-ylsulfonamide (8d):** Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.96 (t, $J = 7.4$ Hz, 3H), 1.36 (sext, $J = 7.4$ Hz, 2H), 1.73–1.82 (m, 2H), 2.13 (q, $J = 7.1$ Hz, 2H), 2.97–3.04 (m, 2H), 3.12 (q, $J = 7.2$ Hz, 2H), 4.39–4.49 (brm, 1H), 4.99–5.09 (m, 2H), 5.79 (dd, $J = 17.2, 10.3, 7.1$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 13.6, 21.5, 25.6, 29.4, 30.7, 42.6, 53.2, 115.6, 137.2. IR (neat) 3289, 2962, 1432, 1322, 1144, 1082 cm$^{-1}$. MS (ESI) calcd for C$_{19}$H$_{20}$NO$_2$S [M + H]$^+$ 266.1209, found 266.1212.

**($1S$)-10-Camphor-$N$-(pent-4-en-1-yl)sulfonamide (8e):** Colorless oil. $^1$H NMR(400 MHz, CDCl$_3$) $\delta$ 0.92 (s, 3H), 1.03 (s, 3H), 1.42–1.50 (m, 1H), 1.71 (quin, $J = 7.3$ Hz, 2H),
1.91–2.09 (m, 3H), 2.10–2.27 (m, 4H), 2.36–2.43 (m, 1H), 2.91 (d, \( J = 15.2 \) Hz, 1H),
3.10–3.24 (m, 2H), 3.39 (d, \( J = 15.2 \) Hz, 1H), 4.97–5.10 (m, 2H), 5.13–5.20 (brm, 1H),
5.80 (ddt, \( J = 17.2, 10.5, 6.9 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 19.5, 19.9, 26.6,
27.0, 29.2, 30.7, 42.8, 42.9, 43.1, 48.8, 49.3, 59.2, 115.4, 137.4, 217.0. IR (neat) 3295,
2959, 1742, 1329, 1146, 1069 cm\(^{-1}\). MS (ESI) calcd for C\(_{15}\)H\(_{26}\)NO\(_3\)S [M + H\(^+\)] 300.1628,
found 300.1624.

**General Procedure for the Intramolecular Aminohydroxylation of N-Alkenyl Sulfonamides (8)** (Table 8, entry 10 and Table 9). To a solution of 8a (59.8 mg, 0.25
mmol) and Oxone® (230.5 mg, 0.375 mmol) in a 1:1 mixture (1.5 mL) of MeCN and H\(_2\)O
was added TsOH·H\(_2\)O (4.8 mg, 0.025 mmol). The solution was stirred at 50 °C for 10 h.
Saturated NaHCO\(_3\) aqueous solution (10 mL) was added to the reaction mixture, and
the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed
with brine (10 mL) and dried over Na\(_2\)SO\(_4\). The organic phase was concentrated under
reduced pressure and the crude product was purified by silica-gel column chromatography (eluent: hexane/AcOEt = 2/1)
to give desired product 9a (63.8 mg, >99% yield) as a colorless oil.

\((\pm)-[1-[(4-Fluorophenyl)sulfonyl]pyrrolidin-2-yl]methanol (9b):\) White solid (58.3 mg,
90% yield) mp 69–70 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.45–1.54 (m, 1H), 1.65–1.77
(m, 2H), 1.77–1.89 (m, 1H), 2.68 (brs, 1H), 3.24 (dt, \( J = 10.4, 7.1 \) Hz, 1H), 3.48 (dt, \( J =
10.4, 6.2 \) Hz, 1H), 3.59–3.66 (m, 1H), 3.66–3.76 (m, 2H), 7.19–7.28 (m, 2H), 7.85–7.92 (m,
2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.2, 28.9, 50.0, 61.9, 65.7, 116.5 (d, \( ^{13}\)C–F = 23.0
Hz) (2C), 130.2 (d, \( ^{13}\)C–F = 9.6 Hz) (2C), 133.0 (d, \( ^{13}\)C–F = 3.8 Hz), 165.3 (d, \( ^{13}\)C–F = 256.8
Hz). IR (KBr) 3534, 1493, 1332, 1237, 1155, 1093, 1042 cm\(^{-1}\). MS (ESI) calcd for
C\(_{11}\)H\(_{14}\)FNNaO\(_3\)S [M + Na\(^+\)] 282.0571, found 282.0567.

\((\pm)-[1-[(4-Nitrophenyl)sulfonyl]pyrrolidin-2-yl]methanol (9c):\) Yellow solid (55.8 mg,
78% yield) mp 93–94 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.50–1.60 (m, 1H), 1.67–1.77
(m, 1H), 1.77–1.96 (m, 2H), 2.51 (brs, 1H), 3.27 (dt, \( J = 10.6, 7.1 \) Hz, 1H), 3.53 (dt, \( J = 10.6,
6.3 \) Hz, 1H), 3.64–3.78 (m, 3H), 8.06 (d, \( J = 8.9 \) Hz, 2H), 8.40 (d, \( J = 8.9 \) Hz, 2H). \(^{13}\)C
NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.2, 28.8, 50.0, 62.1, 65.5, 124.4 (2C), 128.7 (2C), 142.9,
150.2. IR (neat) 3567, 1532, 1349, 1163, 1095 cm\(^{-1}\). MS (ESI) calcd for C\(_{11}\)H\(_{15}\)N\(_2\)O\(_5\)S [M +
H\(^+\)] 287.0696, found 287.0694.

\((\pm)-[1-(Butylsulfonyl)pyrrolidin-2-yl]methanol (9d):\) Colorless oil (53.7 mg, 97% yield).
1H NMR (400 MHz, CDCl3) δ 0.96 (t, J = 7.6 Hz, 3H), 1.47 (sext, J = 7.6 Hz, 2H), 1.78−1.92 (m, 4H), 1.92−2.00 (m, 1H), 2.01−2.12 (m, 1H), 2.67 (brs, 1H), 2.99 (dd, J = 9.0, 7.1 Hz, 2H), 3.35−3.49 (m, 2H), 3.55−3.69 (m, 2H), 3.82−3.90 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 13.6, 21.7, 24.8, 25.1, 29.1, 48.9, 49.5, 61.5, 65.8. IR (neat) 3504, 1327, 1144, 1050 cm⁻¹. MS (ESI) calcd for C9H20NO3S [M + H]+ 222.1158, found 222.1161.

[1-(1S)-10-Camphorsulfonylpyrrolidin-2-yl]methanol (9e, Diastereomeric Mixture): Colorless oil (71.7 mg, 91% yield, dr = 55:45). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.90 (s, 3H), 1.14 (s, 3H), 1.38−1.49 (m, 1H), 1.61−1.72 (m, 1H), 1.81−2.16 (m, 7H), 2.34−2.44 (m, 1H), 2.47−2.59 (m, 1H), 2.81 (brs, 1H), 2.83 (d, J = 14.6 Hz, 1H), 3.42 (d, J = 14.6 Hz, 1H), 3.45−3.56 (m, 2H), 3.57−3.76 (m, 2H), 3.90−3.98 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 19.9, 20.1, 24.8, 25.4, 27.0, 29.3, 42.7, 42.9, 44.6, 48.2, 49.9, 58.5, 61.9, 65.8, 215.7. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.90 (s, 3H), 1.13 (s, 3H), 1.38−1.49 (m, 1H), 1.61−1.72 (m, 1H), 1.81−2.16 (m, 7H), 2.34−2.44 (m, 1H), 2.47−2.59 (m, 1H), 2.91 (d, J = 14.6 Hz, 1H), 2.92 (brs, 1H), 3.36 (d, J = 14.6 Hz, 1H), 3.39−3.45 (m, 1H), 3.45−3.56 (m, 1H), 3.57−3.76 (m, 2H), 3.90−3.98 (m, 1H). 13C NMR (100 MHz, CDCl3) δ 19.9, 20.1, 25.0, 25.4, 27.0, 29.0, 42.7, 42.9, 45.8, 48.0, 49.6, 58.4, 62.1, 65.6, 216.0. IR (neat) 3502, 1743, 1146, 1050 cm⁻¹. MS (ESI) calcd for C15H26NO4S [M+ H]+ 316.1577, found 316.1572.

[(5S)-5-Methyl-1-tosylpyrrolidin-2-yl]methanol (9f, Diastereomeric Mixture). Colorless oil (63.2 mg, 94% yield, dr = 50:50). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 1.17 (d, J = 6.6 Hz, 3H), 1.56−1.66 (m, 1H), 1.79−1.89 (m, 1H), 2.02−2.19 (m, 2H), 2.43 (s 3H), 2.60 (brs, 1H), 3.58−3.78 (m, 3H), 4.16−4.25 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 20.2, 21.5, 27.9, 31.8, 57.8, 61.3, 65.5, 127.1 (2C), 129.6 (2C), 138.4, 143.2. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 1.34 (d, J = 6.4 Hz, 3H), 1.43−1.54 (m, 2H), 1.55−1.78 (m, 2H), 2.44 (s, 3H), 2.87 (brs, 1H), 3.58−3.67 (m, 2H), 3.67−3.85 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 23.2, 27.2, 31.7, 58.3, 63.3, 66.1, 127.6 (2C), 129.8 (2C), 134.3, 143.7. IR (neat) 3512, 1332, 1156, 1095, 1049 cm⁻¹. MS (ESI) calcd for C13H20NO3S [M + Na]+ 270.1158, found 270.1155.

[(5R)-5-Isopropyl-1-tosylpyrrolidin-2-yl]methanol (9g): The diastereomers were separated by column chromatography. White solid (67.6 mg, 91% yield, dr = 52:48). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.92 (d, J = 7.9 Hz, 3H), 1.02 (d, J = 7.9 Hz, 3H), 1.16−1.27 (m, 1H), 1.50−1.69 (m, 3H), 1.92−2.02 (m, 1H), 2.44 (s, 3H), 3.00
(brs, 1H), 3.49 (td, J = 7.6, 3.9 Hz, 1H), 3.58–3.68 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 17.8, 20.1, 21.5, 25.7, 27.1, 31.4, 63.0, 66.0, 68.4, 127.7 (2C), 129.7 (2C), 134.3, 143.7. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.49 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 1.68–1.76 (m, 1H), 1.77–2.02 (m, 3H), 2.42 (s, 3H), 2.36–2.46 (m, 1H), 2.61–2.68 (m, 1H), 3.76–3.85 (m, 3H), 3.94–4.00 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 15.6, 19.8, 21.5, 23.8, 29.6, 29.8, 63.0, 65.3, 66.5, 126.8 (2C), 129.5 (2C), 138.5, 143.0. IR (KBr) 3520, 1469, 1328, 1155, 1045 cm⁻¹. MS (ESI) calcd for C₁₅H₂₄NO₃S [M+H]+ 298.1471, found 298.1472.

(±)-(2-Tosyl-2-azaspiro[4.5]decan-3-yl)methanol (9j): Colorless oil (79.2 mg, 98% yield). 1H NMR (400 MHz, CDCl3) δ 0.51–0.59 (m, 1H), 0.66–0.76 (m, 1H), 1.05–1.47 (m, 8H), 1.51 (dd, J = 12.9, 9.7 Hz, 1H), 1.73 (dd, J = 12.9, 7.5 Hz, 1H), 2.44 (s, 3H), 3.16 (d, J = 11.2 Hz, 1H), 3.29 (dd, J = 8.3, 5.1 Hz, 1H), 3.33 (d, J = 11.2 Hz, 1H), 3.51–3.59 (m, 1H), 3.66–3.74 (m, 1H), 3.74–3.83 (m, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 22.7, 23.6, 25.8, 27.5, 30.8, 35.6, 59.7, 62.1, 66.6, 127.3 (2C), 129.7 (2C), 134.0, 143.8. IR (neat) 3500, 1335, 1157, 1095, 1049 cm⁻¹. MS (ESI) calcd for C₁₅H₂₄NO₃S [M+H]+ 324.1628, found 324.1624.

(±)-(cis-1-Tosyloctahydro-1H-indol-2-yl)methanol (9k, Diastereomeric Mixture): Colorless oil (69.6 mg, 90% yield, dr = 54:46). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.99–1.02 (m, 1H), 1.02–1.30 (m, 2H), 1.31–1.75 (m, 5H), 1.85–1.88 (m, 1H), 2.21–2.24 (m, 2H), 2.43 (s, 3H), 2.64 (t, J = 6.8 Hz, 1H), 3.62–3.73 (m, 1H), 3.75–3.86 (m, 2H), 3.96 (dt, J = 11.0, 5.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 19.8, 21.5, 23.6, 25.8, 27.5, 30.8, 35.6, 59.7, 62.1, 66.6, 127.3 (2C), 129.6 (2C), 137.9, 143.2. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 1.02–1.30 (m, 3H), 1.31–1.75 (m, 7H), 1.92–2.03 (m, 1H), 2.44 (s, 3H), 3.17 (dd, J = 8.2, 4.8 Hz, 1H), 3.52–3.61 (m, 1H), 3.62–3.73 (m, 2H), 3.73–3.86 (m, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 20.1, 21.5, 24.3, 25.6, 30.9, 31.8, 36.0, 61.7, 62.6, 66.3, 127.4 (2C), 129.8 (2C), 134.6, 143.6. IR (neat) 3502, 1335, 1157, 1095, 1049 cm⁻¹. MS (ESI) calcd for C₁₆H₂₆NO₃S [M+H]+ 348.1693, found 348.1694.

(±)-(trans-1-Tosyloctahydro-1H-indol-2-yl)methanol (9l, Diastereomeric Mixture): Colorless oil (60.3 mg, 78% yield, dr = 66:34). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.84–1.47 (m, 6H), 1.57–1.74 (m, 3H), 1.75–1.88 (m, 2H), 2.35 (td, J = 10.5,
3.4 Hz, 1H), 2.45 (s, 3H), 2.49–2.59 (m, 1H), 3.61–3.77 (m, 3H), 7.35 (d, 1H), 7.71 (d, 1H), 2.45 (s, 3H), 2.49–2.59 (m, 1H), 3.61–3.77 (m, 3H), 7.35 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 24.6, 25.2, 29.8, 32.6, 33.1, 43.8, 62.1, 66.9, 67.4, 128.0 (2C), 129.7 (2C), 133.0, 143.7. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.84–1.47 (m, 6H), 1.57–1.74 (m, 3H), 1.75–1.88 (m, 2H), 2.05–2.15 (m, 1H), 2.43 (s, 3H), 2.84 (dd, J = 11.6, 10.5, 3.4 Hz, 1H), 3.04 (brs, 1H), 3.77–3.85 (m, 1H), 4.00–4.08 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 24.6, 25.2, 29.8, 32.6, 33.1, 43.8, 62.1, 66.9, 67.4, 128.0 (2C), 129.7 (2C), 133.0, 143.7. IR (neat) 3505, 1340, 1157, 1095 cm⁻¹. MS (ESI) calcd for C16H24NO3S [M + H]+ 310.1471, found 310.1468.

(--)-syn-1-(1-Tosylpyrrolidin-2-yl)ethanol (9n): White solid (61.2 mg, 91% yield, dr = 99:<1) mp 73–74 °C. 1H NMR (400 MHz, CDCl3) δ 1.18 (d, J = 6.2 Hz, 3H), 1.28–1.39 (m, 1H), 1.51–1.63 (m, 2H), 1.66–1.77 (m, 1H), 2.44 (s, 3H), 3.32–3.45 (m, 3H), 3.45–3.53 (m, 1H), 3.67–3.76 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 19.4, 21.5, 24.5, 28.4, 49.8, 66.4, 69.7, 127.6 (2C), 129.8 (2C), 134.2, 143.9. IR (KBr) 3523, 1327, 1153, 1105, 1079 cm⁻¹. MS (ESI) calcd for C16H24NO3S [M + H]+ 310.1471, found 310.1468.

(--)-anti-1-(1-Tosylpyrrolidin-2-yl)ethanol (9o): Colorless oil (55.2 mg, 82% yield, dr = 77:23). 1H NMR (400 MHz, CDCl3) δ 1.17 (d, J = 6.4 Hz, 3H), 1.24–1.32 (m, 1H), 1.59–1.69 (m, 1H), 1.69–1.89 (m, 2H), 2.44 (s, 3H), 2.62 (brs, 1H), 3.32–3.43 (m, 2H), 3.48–3.54 (m, 1H), 4.15–4.24 (m, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 18.3, 21.5, 24.5, 28.4, 49.8, 65.7, 69.0, 127.6 (2C), 129.7 (2C), 133.9, 143.7. IR (KBr) 3506, 1337, 1158, 1092, 999 cm⁻¹. MS (ESI) calcd for C16H24NO3S [M + H]+ 310.1471, found 310.1468.

(--)-(2-Methyl-1-tosylpyrrolidin-2-yl)methanol (9p): White solid (52.5 mg, 78% yield) mp 64–65 °C. 1H NMR (400 MHz, CDCl3) δ 1.25 (s, 3H), 1.58–1.68 (m, 1H), 1.71–1.93 (m, 2H), 2.14 (dt, J = 12.4, 7.9 Hz, 1H), 2.43 (s, 3H), 2.66 (brs, 1H), 3.33–3.41 (m, 1H), 3.48 (dt, J = 9.4, 7.2 Hz, 1H), 3.59 (dd, J = 11.7, 5.4 Hz, 1H), 3.89 (dd, J = 11.7, 3.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 22.2, 22.4, 38.1, 50.8, 68.9, 69.1, 127.2 (2C), 129.6 (2C), 137.8, 143.2. IR (KBr) 3527, 1325, 1152, 1094, 1052 cm⁻¹. MS (ESI) calcd for C16H24NO3S [M + Na]+ 292.0978, found 292.0970.
General Procedure for the Transformation of N-Sulfonyl Prolinol Derivatives (9) into
N-Sulfonyl Proline Derivatives (10) by Oxidation with a DIB/TEMPO System (Scheme 3).
To a solution of 9a (63.8 mg, 0.25 mmol) and DIB (177.1 mg, 0.55 mmol) in a 1:1 mixture (1.5 mL) of MeCN and H2O was added TEMPO (3.9 mg, 0.025 mmol), and the solution was stirred at room temperature for 12 h. Saturated NaHCO3 aqueous solution (10 mL) was added to the reaction mixture. The product was basified to pH 10 with 1M NaOH aq., and washed with AcOEt (15 mL × 3). The aqueous layer was acidified to pH 3 with 1M HCl aq., extracted with CHCl3 (15 mL × 3), and dried over Na2SO4. The organic phase was concentrated under reduced pressure to give the desired product 10a (59.2 mg, 88% yield) as a white solid without further purification.

(5R)-5-Isopropyl-1-tosylpyrrolidine-2-carboxylic acid (10g, Diastereomeric Mixture):
White solid (72.3 mg, 93% yield, dr = 55:45). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.93 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.34−1.45 (m, 1H), 1.71−1.87 (m, 2H), 2.02−2.17 (m, 2H), 2.45 (s, 3H), 3.53 (dd, J = 11.9, 7.1 Hz, 1H), 4.17 (dd, J = 8.3, 6.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 9.25 (brs, 1H). 13C NMR (100 MHz, CDCl3) δ 17.2, 20.1, 21.6, 26.0, 28.3, 31.1, 62.0, 68.1, 127.7 (2C), 129.9 (2C), 133.8, 144.3, 175.2. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 0.51 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 1.70−1.84 (m, 1H), 1.96−2.19 (m, 3H), 2.24−2.37 (m, 1H), 2.43 (s, 3H), 3.98−4.04 (m, 1H), 4.51 (d, J = 7.3 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 9.25 (brs, 1H). 13C NMR (100 MHz, CDCl3) δ 14.8, 19.7, 21.5, 23.7, 29.5, 29.8, 62.3, 64.9, 127.0 (2C), 129.4 (2C), 138.1, 143.2, 178.5. IR (KBr) 2965, 1528, 1345, 1159, 1093 cm−1. MS (ESI) calcd for C15H22NO4S [M + H]+ 312.1264, found 312.1258.

(±)-4,4-Dimethyl-1-tosylpyrrolidine-2-carboxylic acid (10i):
White solid (70.6 mg, 95% yield). 1H NMR (400 MHz, CDCl3) δ 0.74 (s, 3H), 1.09 (s, 3H), 1.91−2.02 (m, 2H), 2.44 (s, 3H), 3.30 (d, J = 10.0 Hz, 1H), 3.21 (t, J = 10.0 Hz, 1H), 4.29 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 10.43 (brs, 1H). 13C NMR (100 MHz, CDCl3) δ 21.6, 25.5, 25.7, 38.8, 44.2, 60.4, 60.7, 127.7 (2C), 129.7 (2C) 134.4, 144.0, 177.2. IR (KBr) 2963, 1729, 1345, 1159, 1093 cm−1. MS (ESI) calcd for C14H20NO4S [M + H]+ 298.1108, found 298.1104.

(±)-2-Tosyl-2-azaspiro[4.5]decane-3-carboxylic acid (10j):
Colorless oil (75.9 mg, 80% yield). 1H NMR (400 MHz, CDCl3) δ 0.86−0.95 (m, 1H), 0.95−1.05 (m, 1H), 1.14−1.51 (m, 9H), 1.88−1.97 (m, 1H), 1.97−2.06 (m, 1H), 2.44 (s, 3H), 3.22 (d, J = 10.6 Hz, 1H),
3.25 (d, $J = 10.6$ Hz, 1H), 4.22 (t, $J = 8.2$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.79 (d, $J = 8.3$ Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 21.5, 22.9, 23.5, 25.6, 34.1, 35.3, 42.2, 42.7, 58.1, 59.8, 127.7 (2C), 129.7 (2C), 134.2, 144.0, 176.8. IR (neat) 3545, 1729, 1346, 1156, 1093, 1056 cm$^{-1}$. MS (ESI) calcd for C17H24NO4S [M + H]$^+$ 338.1421, found 338.1411.

(±)-cis-1-Toslyoctahydro-1H-indole-2-carboxylic acid (10k, Diastereomeric mixture):
White solid (80.8 mg, >99% yield, dr = 51:49). Major-diastereomer: 1H NMR (400 MHz, CDCl3) δ 1.01–1.35 (m, 3H), 1.36–1.72 (m, 4H), 1.72–1.82 (m, 1H), 2.03–2.13 (m, 2H), 2.19 (td, $J = 12.6$, 8.9 Hz, 1H), 2.45 (s, 3H), 2.54–2.65 (m, 1H), 3.66 (dt, $J = 11.0$, 6.3 Hz, 1H), 4.20 (t, $J = 8.9$ Hz, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 20.3, 21.5, 23.4, 25.6, 29.5, 32.4, 37.3, 59.1, 60.5, 127.6 (2C), 129.5 (2C), 137.7, 143.4, 178.3. Minor-diastereomer: 1H NMR (400 MHz, CDCl3) δ 1.01–1.35 (m, 3H), 1.36–1.72 (m, 6H), 1.82–1.92 (m, 1H), 1.94 (dd, $J = 13.1$, 6.3 Hz, 1H), 2.33 (td, $J = 13.1$, 9.6 Hz, 1H), 2.43 (s, 3H), 3.75–3.86 (m, 1H), 4.40 (d, $J = 9.6$ Hz, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.79 (d, $J = 8.3$ Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 20.1, 21.5, 23.7, 25.6, 28.5, 32.6, 35.8, 59.7, 60.7, 127.6 (2C), 129.8 (2C), 135.0, 143.9, 177.6. IR (KBr) 2932, 1725, 1340, 1157, 1096 cm$^{-1}$. MS (ESI) calcd for C16H22NO4S [M + H]$^+$ 324.1264, found 324.1256.

Transformation of N-Tosyl Proline (10a) into Proline Ethyl Ester (12a) by Detosylation under Mild Conditions (Scheme 8).
To a solution of N-tosyl proline (10a) (53.8 mg, 0.20 mmol) and K2CO3 (55.2 mg, 0.40 mmol) in DMF (1.0 mL) was added EtI (24.1 µL, 0.30 mmol). The solution was stirred at room temperature for 14 h under argon atmosphere. 1M HCl solution (3 mL) was added to the reaction mixture, and the product was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na2SO4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica-gel column chromatography (eluent: hexane/AcOEt = 4/1) to give N-tosyl proline ethyl ester (11a) (59.4 mg, >99% yield) as a white solid. The solution of N-tosyl proline ethyl ester (11a) (74.3 mg, 0.25 mmol), phenol (47.0 mg, 0.50 mmol), and 25% HBr in acetic acid (1 mL) was stirred at room temperature for 24 h under argon atmosphere. This reaction mixture was concentrated under reduced pressure to give proline ethyl ester (12a) (52.6 mg, 94%) as a brown oil.

(±)-Ethyl pyrrolidine-2-carboxylate hydrobromide (12a). 1H NMR (400 MHz, CDCl3) δ 1.34 (t, $J = 7.3$ Hz, 3H), 2.02–2.27 (m, 3H), 2.41–2.53 (m, 1H), 3.53–3.69 (m, 2H), 4.32 (q,
$J = 7.3 \text{ Hz, } 2\text{H}, \text{ } 4.49-4.60 \text{ (m, } 1\text{H}), \text{ } 8.52 \text{ (brs, } 1\text{H}), \text{ } 10.3 \text{ (brs, } 1\text{H}).$ $^{13}\text{C NMR (100 MHz, CDCl}_3) \delta \text{ } 14.1, 23.7, 28.8, 46.2, 59.3, 63.3, 168.7. \text{ IR (neat) } 3427, 1739, 1630, 1241, 1043 \text{ cm}^{-1}. \text{ MS (ESI) calcd for } \text{C}_7\text{H}_{14}\text{NO}_2 [M]^+ 144.1019, \text{ found 144.1015.}$
References


(11) (a) Röben, C.; Souto, J. A.; González, Y.; Lishchynskyi, A.; Muñiz, K. Angew.


(13) Treatment of $N$-(3-(oxiran-2-yl)propyl)tosylamide with TsOH·H$_2$O (10 mol%) in a mixture of MeCN and H$_2$O (1:1) at room temperature for 24 h gave 2a in >99% yield.


3. Preparation of $\alpha$-Bromoketones and Thiazoles from Ketones with NBS and Thioamides in Ionic Liquids.

Introduction

Thiazoles are one of the most important heterocycles and known for their broad spectrum of biological activities. Many natural and synthetic molecules containing the thiazole moiety play a significant role in the pharmaceutical industry due to their anti-inflammatory, anti-HIV, anti-bacterial, anti-cancer properties. Today, there are many methods for the preparation of the thiazole moiety. One of the most excellent and efficient methods is the Hantzsch thiazole synthesis that employs the reaction of $\alpha$-haloketones or $\alpha$-tosyloxyketones with thioamides. For the preparation of $\alpha$-bromoketones from ketones, NBS (N-bromosuccinimide) is well used, whereas HTIB [(hydroxy)(tosyloxy)iodobenzene] is the sole reagent for the direct preparation of $\alpha$-tosyloxyketones from ketones. On the other hand, ionic liquids have grown in popularity as organic reaction media due to the promotion of ionic reactions and in view of environmental safety. Ionic liquids offer interesting and useful features that are advantageous to organic reactions such as negligible vapor pressure, nonflammability, high thermal stability, and easy reusability. In this regard, ionic liquids have been successfully used in the Friedel-Crafts reaction, hydrogenation, Diels-Alder reactions, Mizoroki-Heck, Suzuki-Miyaura, Sonogashira, and olefin metathesis reactions, Michael additions, oxidation, condensation reaction, formation of imines, 1,2-rearrangement, esterification of carboxylic acids and carboxylates, Williamson ether synthesis, and the Grignard reaction. The author laboratory has reported efficient methods for the esterification of carboxylic acids and phosphonic acids with trialkyl orthoacetate in ionic liquid, the demethylation of $N,N$-dimethylanilines with phenyl chloroformate in ionic liquids, and the 3-exor-tet cyclization of 2,2-disubstituted 1,3-dihalopropanes with indium in ionic liquid. The $\alpha$-bromination of $\beta$-dicarbonyls and cyclic ketones with NBS in ionic liquids, and the aromatic ring bromination with NBS in ionic liquids have been reported as well. However, to the best of his knowledge, there are no synthetic studies that deal with the preparation of thiazoles from ketones with NBS and thioamides in ionic liquids. Here, as a part of his synthetic study of ionic liquids, The author would like to report the preparation of $\alpha$-bromoketones and thiazoles from ketones, with NBS and thioamides in typical room-temperature ionic liquids.
Result and discussion

The α-bromination of ketones 13 with NBS in the presence of a catalytic amount of p-toluenesulfonic acid mono hydrate (p-TsOH · H₂O) was carried out at room temperature in both chloroform and typical room-temperature ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim] PF₆), N-butylnmethyl-pyrrolidinium bis(trifluoromethanesulfonyl)imidate ([bmpy]Tf₂N), and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄), as shown in Table 7. As a result, the corresponding α-bromoketones 14 were obtained in good to high yields in chloroform, [bmim]PF₆, and [bmpy]Tf₂N, respectively. In contrast, the α-bromination of ketones did not proceed at all in [bmim]BF₄. It is probable that the proton derived from p-TsOH could not promote the formation of enol forms of ketones due to the interaction between the proton of p-TsOH and BF₄⁻. Practically, chemical shift of a hydrogen atom

Table 7. α-Bromination of Ketones (13) in Several Ionic Liquids and CHCl₃.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield of 14 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>96</td>
</tr>
<tr>
<td>13b</td>
<td>84</td>
</tr>
<tr>
<td>13c</td>
<td>90</td>
</tr>
<tr>
<td>13d</td>
<td>93</td>
</tr>
<tr>
<td>13e</td>
<td>85</td>
</tr>
<tr>
<td>13f</td>
<td>74</td>
</tr>
<tr>
<td>13g</td>
<td>83</td>
</tr>
<tr>
<td>13h</td>
<td>81</td>
</tr>
<tr>
<td>13i</td>
<td>78</td>
</tr>
<tr>
<td>13j</td>
<td>73</td>
</tr>
<tr>
<td>13k</td>
<td>82</td>
</tr>
<tr>
<td>13a</td>
<td>0</td>
</tr>
<tr>
<td>13b</td>
<td>0</td>
</tr>
<tr>
<td>13c</td>
<td>0</td>
</tr>
<tr>
<td>13d</td>
<td>0</td>
</tr>
<tr>
<td>13e</td>
<td>95</td>
</tr>
<tr>
<td>13f</td>
<td>75</td>
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<tr>
<td>13g</td>
<td>92</td>
</tr>
<tr>
<td>13h</td>
<td>74</td>
</tr>
<tr>
<td>13i</td>
<td>68</td>
</tr>
<tr>
<td>13j</td>
<td>68</td>
</tr>
<tr>
<td>13k</td>
<td>83</td>
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<tr>
<td>13a</td>
<td>67</td>
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<tr>
<td>13b</td>
<td>57</td>
</tr>
<tr>
<td>13c</td>
<td>64</td>
</tr>
<tr>
<td>13d</td>
<td>66</td>
</tr>
</tbody>
</table>
at 2-position of [bmim]BF₄ is 9.42 ppm (CDCl₃, TMS), and is lower field than that of [bmim]PF₆ (8.42 ppm, CDCl₃, TMS). This suggests that BF₄⁻ in [bmim]BF₄ interacts strongly with a proton of p-TsOH. Moreover, the yields of α-bromoketones in [bmim]PF₆ and [bmpy]Tf₂N are higher overall than those in chloroform, especially when propiophenone and nonanophenone were used as substrate (13f, 13g). When an ionic liquid such as [bmim]PF₆ was used, α-bromoketone was obtained in good yields with good purity (>80%) by simple ether extraction of the reaction mixture and the ionic liquid reaction medium could be reused for the same reaction up to the 7th time while maintaining the high yields of α-bromoketone, as shown in Table 8.

<table>
<thead>
<tr>
<th>Reuse</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>95</td>
</tr>
</tbody>
</table>

Then, the one-pot conversion of ketones 13 to thiazoles 15 in both chloroform and ionic liquids, such as [bmim]PF₆ and [bmpy]Tf₂N, was studied, as shown in Table 9. After the α-bromination of ketones with NBS, thioamide and potassium carbonate were added to the reaction mixture, and the obtained mixture was stirred at room temperature. Overall, the yields in [bmim]PF₆ and [bmpy]Tf₂N were higher than those in chloroform, particularly, when propiophenone with thiobenzamide (15f), acetophenone with p-methoxythiobenzamide (15a), and acetophenone with thioacetamide (15o) were used. In the reaction with acetophenone in [bmim]PF₆, thiazoles were obtained in good yields with moderate purity (>70%) by ether extraction, and the ionic liquid reaction medium could be reused for the same reaction, maintaining the good yields of thiazole up to the 5th time, as shown in Table 10.

In conclusion, typical room temperature ionic liquids, such as [bmim] PF₆ and [bmpy]Tf₂N could be used for the conversion of ketones to α-bromoketones with NBS and the conversion of ketones to thiazoles with NBS and subsequently thioamides in a one-pot manner. α-Bromoketones and thiazoles could be obtained in good yields with good purity by simple ether extraction, and the ionic liquid reaction media could be reused for the same reaction while maintaining good yields and purity of the products. The present method offers a green approach to the preparation of α-bromoketones and thiazoles in good yields with good purity from ketones with NBS and subsequently
thioamides at room temperature.

Table 9. One-pot Synthesis of Thiazols (13) in Several Ionic Liquid and CHCl₃.

<table>
<thead>
<tr>
<th>Product, Yield of 15 (%)</th>
<th>[Bmim]PF₆</th>
<th>[Bmpy]Tf₂N</th>
<th>CHCl₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>86</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>15b</td>
<td>94</td>
<td>96</td>
<td>73</td>
</tr>
<tr>
<td>15c</td>
<td>96</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>15d</td>
<td>89</td>
<td>69</td>
<td>73</td>
</tr>
<tr>
<td>15e</td>
<td>85</td>
<td>83</td>
<td>30</td>
</tr>
<tr>
<td>15f</td>
<td>73</td>
<td>74</td>
<td>30</td>
</tr>
<tr>
<td>15h</td>
<td>99</td>
<td>-</td>
<td>94</td>
</tr>
<tr>
<td>15i</td>
<td>77ᵃ</td>
<td>71</td>
<td>-</td>
</tr>
<tr>
<td>15j</td>
<td>99</td>
<td>64</td>
<td>90</td>
</tr>
<tr>
<td>15k</td>
<td>84</td>
<td>85</td>
<td>83</td>
</tr>
<tr>
<td>15l</td>
<td>61</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>15m</td>
<td>26</td>
<td>78</td>
<td>44</td>
</tr>
</tbody>
</table>

ᵃ Reaction temperature was 50°C.
Table 10: Reuse of [Bmim]PF$_6$ for preparation of 2,4-Diphenylthiazol (15c)

\[
\begin{align*}
1\) \text{TsCl} + H_2O (20 mol%), NBS (1.2 equiv.) \\
\text{[Bmim]PF}_6 (1.5 mL), r.t., 13 h \\
\text{2) PhC(S)NH}_2 (1.2 equiv.) K_2CO_3 (1.1 equiv.) \\
r.t., 5 h
\end{align*}
\]

<table>
<thead>
<tr>
<th>Reuse</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield(%)</td>
<td>96</td>
<td>97</td>
<td>91</td>
<td>85</td>
<td>89</td>
<td>96</td>
</tr>
</tbody>
</table>
Experimental Section

General procedure

$^1$H NMR and $^{13}$C NMR spectra were obtained on JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. All chemical shifts were expressed in ppm, $\delta$ units down field from TMS (Me$_4$Si). Mass spectra were recorded on JEOL-HX-110 and JEOL-JMS-AT15 spectrometers. Melting points were determined on Yamato melting points apparatus Model MP-21. Silica Gel 60 (Kanto Kagaku Co.) and Wakogel B5F were used for column chromatography and preparative TLC, respectively.

Typical Procedure for Conversion of Acetophenone (13a) into $\alpha$-Bromoacetophenone (14a) with NBS and $p$-TsOH H$_2$O in Ionic Liquids: To a solution of acetophenone (13a, 1 mmol) in $[\text{Bmim}]PF_6$ (1.5 mL) were added $p$-TsOH·H$_2$O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 9.5 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 7). Then, the extract was poured into sat. aq. Na$_2$SO$_3$ solution. The organic layer was dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, $\alpha$-bromoacetophenone was obtained in the crude state. Purity was estimated by $^1$H NMR to be in the range of 70% - 80%. Pure $\alpha$-bromoacetophenone (14a) was obtained by flash short column chromatography on silica gel (CHCl$_3$:Hexane = 1:1) in 90% yield.

Typical Reuse of $[\text{Bmim}]PF_6$:

After the extraction of the reaction mixture with diethyl ether, the ionic liquid was dried with a vacuum pump for 2 h at 80°C. To a solution of acetophenone (1 mmol) in $[\text{Bmim}]PF_6$ (1.5 mL) were added $p$-TsOH·H$_2$O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 9 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 7). Then, extract was poured into sat. aq. Na$_2$SO$_3$ solution. The organic layer was dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, $\alpha$-bromoacetophenone (14a) was obtained in the crude state. Purity was estimated by $^1$H NMR to be in the range of 70% - 80%. Pure $\alpha$-bromoacetophenone was obtained by flash short column chromatography on silica gel (CHCl$_3$:Hexane = 1:1) in 91% yield.

$\alpha$-Bromoacetophenone (14c): mp 54°C - 55°C (lit. 26 mp 49°C - 50°C); IR(Nujol) 2319, 1690, 1594, 1308, 1276, 1199, 991, 745, 685 cm$^{-1}$; $^1$H NMR(500 MHz, CDCl$_3$): $\delta$ = 7.99 (d, 2H, $J$ = 7.4 Hz, ArH), 7.62 (t, 1H, $J$ = 7.4 Hz, ArH), 7.50 (t, 2H, $J$ = 7.4 Hz, ArH), 4.46 (s, 2H, $\text{-CH}_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 191.2, 133.9 (3C), 128.9, 128.8, 30.8.
α-Bromo-4’-chloroacetophenone (14d): mp 101°C - 103°C (lit. mp 95°C - 96°C); IR(Nujol) 3853, 3749, 3648, 1690, 1540, 1507, 1092, 721, 509 cm⁻¹; ¹H NMR(400 MHz, CDCl₃): δ = 7.99 (d, 2H, J = 7.3 Hz, ArH), 7.62 (t, 1H, J = 7.3 Hz, ArH), 7.50 (t, 2H, J = 8.0 Hz, ArH), 4.46 (s, 2H, -CH₂Br); ¹³C NMR (125 MHz, CDCl₃): δ = 190.2, 140.5, 132.2, 130.3, 129.2, 30.3.

α-Bromo-4’-methoxyacetophenone (14a): mp 70°C (lit. mp 69°C - 73°C); IR(Nujol) 3853, 3749, 3648, 2309, 1683, 1598, 1508, 1322, 1306, 1260, 1205, 1170, 1116, 1020, 986, 840, 816, 721 cm⁻¹; ¹H NMR(400 MHz, CDCl₃): δ = 7.97 (d, 2H, J = 7.8 Hz, ArH), 6.96 (d, 2H, J = 7.8 Hz, ArH), 4.40 (s, 2H, -CH₂-), 3.88 (s, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 189.8, 163.9, 131.1, 126.7, 113.9, 55.5, 30.7.

α-Bromo-4’-methylacetophenone (14b): mp 56°C - 58°C (lit. mp 48°C - 50°C); IR(Nujol) 1687, 1608, 1179, 799, 723 cm⁻¹; ¹H NMR(500 MHz, CDCl₃): δ = 7.88 (d, 2H, J = 8.6 Hz, ArH), 7.28 (d, 2H, J = 8.6 Hz, ArH), 4.42 (s, 2H, -CH₂Br), 2.42 (s, 3H, -CH₃) ; ¹³C NMR (125 MHz, CDCl₃): δ = 190.9, 144.9, 131.4, 129.5, 129.0, 30.9, 21.7.

α-Bromo-4’-nitroacetophenone (14e): mp 98°C - 101°C (lit. mp 98°C); IR(Nujol) 3853, 3748, 3647, 2309, 1698, 966, 844, 720 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.35 (d, 2H, J = 8.9 Hz, ArH), 8.16 (d, 2H, J = 8.4 Hz, ArH), 4.46 (s, 2H, -CH₂Br); ¹³C NMR (125 MHz, CDCl₃): δ = 189.8, 150.7, 138.3, 130.0, 124.0, 31.0.

α-Bromopropiophenone (14f): Oil; IR(Neat) 3062, 2978, 2925, 1686, 1595, 1448, 1346, 1238, 1160, 994, 949, 707 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.03 (d, 2H, J = 7.4 Hz, ArH), 7.59 (t, 1H, J = 6.9 Hz, ArH), 5.29 (q, J = 6.30 Hz, 1H, -CH₃), 1.91 (d, J = 6.30 Hz, 3H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 193.2, 134.0, 133.6, 128.8, 128.6, 41.4, 20.0.

α-Bromononanophenone (14g): Oil; IR(Neot) 3062, 2978, 2925, 1686, 1595, 1448, 1346, 1238, 1160, 994, 949, 707 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 8.40 (d, 2H, J = 7.4 Hz, ArH), 7.48 (t, 2H, J = 7.4 Hz, ArH), 5.13 (t, 1H, J = 6.8 Hz, -CHBr), 2.24-2.07 (m, 2H, -CH₂), 1.53-1.48 (m, 1H, -CH₃), 1.43-1.27 (m, 9H, -CH₂), 0.89-0.86 (t, 3H, J = 6.8 Hz, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 193.3, 134.5, 133.6, 128.8, 128.7, 47.3, 33.5, 31.6, 29.1, 29.0, 27.5, 22.5, 14.0.

2-(α-Bromacetyl)thiophene (14h): Oil; IR(Neot) 3544, 3297, 3091, 2942, 2469, 2319,
1660, 1517, 1412, 1355, 1289, 1238, 1193, 1112, 1079, 1061, 1041, 972, 940, 885, 859, 
727, 686, 664, 632, 614 cm⁻¹; ¹H NMR(500 MHz, CDCl₃): δ = 7.81 (d, 1H, J = 4.0 Hz, 
thiophene), 7.72 (d, 1H, J = 4.6 Hz, thiophene), 7.17 (t, 1H, J = 4.5 Hz, thiophene), 4.36 
s (2H, -CH₂Br); ¹³C NMR (125 MHz, CDCl₃): δ = 184.3, 140.7, 135.2, 133.5, 128.3, 123.8, 
119.3, 111.2, 107.9, 106.1, 104.1, 97.2, 94.0, 88.5, 85.9, 72.7, 68.6, 66.4, 63.2, 61.4 cm⁻¹; ¹H 
NMR(400 MHz, CDCl₃): δ = 4.44 (t, 1H, J = 5.1 Hz, -CHBr-), 3.01 - 2.95 (m, 1H, -CH₂-), 
2.36 - 2.29 (m, 2H, -CH₂-), 2.27 - 2.19 (m, 1H, -CH₂-), 2.06 - 1.92 (m, 2H, -CH₂-), 1.85 - 
1.70 (m, 2H, -CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 203.4, 53.4, 37.9, 36.7, 26.7, 22.1

α-Bromocyclohexanone (14i): Oil; IR(Neat) 2927, 2867, 1715, 1448, 1430, 962 cm⁻¹; ¹H 
NMR(400 MHz, CDCl₃): δ = 4.44 (t, 1H, J = 5.1 Hz, -CHBr-), 3.01 - 2.95 (m, 1H, -CH₂-), 
2.36 - 2.29 (m, 2H, -CH₂-), 2.27 - 2.19 (m, 1H, -CH₂-), 2.06 - 1.92 (m, 2H, -CH₂-), 1.85 - 
1.70 (m, 2H, -CH₂); ¹³C NMR (125 MHz, CDCl₃): δ = 206.2, 53.6, 39.3, 34.2, 29.5, 26.7, 24.9.

α-Bromocycloheptanone (14j): Oil; IR(Neat) 2933, 2857, 1709, 1454, 1322, 1186, 1159, 
935 cm⁻¹; ¹H NMR(400 MHz, CDCl₃): δ = 4.38 (q, 1H, J = 4.6 Hz, -CHBr-), 2.89 - 2.82 (m, 
1H, -CH-), 2.49 (qd, 1H, J = 8.0 Hz, J = 2.96, -CH-), 2.40 - 2.32 (m, 1H, -CH-), 2.06 - 1.90 
(m, 3H, -CH-), 1.81 - 1.73 (m, 1H, -CH-), 1.62 - 1.51 (m, 2H, -CH-), 1.43 - 1.34 (m, 1H, 
-CH-); ¹³C NMR (100 MHz, CDCl₃): δ = 206.2, 53.6, 39.3, 34.2, 29.5, 26.7, 24.9.

5-Bromoundecan-6-one (14k): Oil; IR (Neat) 2958, 2860, 1717, 1464, 1406, 1377, 1241, 
1125, 1053, 731; ¹H NMR (400 MHz, CDCl₃): δ = 4.23 (dd, 1H, J = 6.6 Hz, J = 8.2 
Hz, -CHBr-), 2.74 - 2.58 (m, 2H, -CH₂-), 2.04 - 1.88 (m, 2H, -CH₂-), 1.62 (quant, 2H, J = 
7.3 Hz, -CH₂-), 2.04 - 1.27 (m, 8H, -CH₂-), 0.90 (q, J = 5.5 Hz, 6H, -CH₃); ¹³C NMR (100 
MHz, CDCl₃): δ = 204.4, 53.7, 38.9, 33.1, 31.2, 29.4, 23.6, 22.4, 22.1, 13.9, 13.8.

Typical Procedure for Conversion of Acetophenone (13a) into 2,4-Diphenylthiazole (15c) 
in Ionic Liquid with NBS and Benzthioamide: To a solution of acetophenone (13a) (1 
mmol) in [Bmim]PF₆ (1.5 mL) were added p-TsOH·H₂O (0.2 mmol) and NBS (1.2 mmol). 
The mixture was stirred for 9 h at room temperature. Then, benzthioamide (1.2 mmol) 
and K₂CO₃ (1.1 mmol) were added to the reaction mixture and the obtained mixture was 
stirred for 5 h at room temperature. After the reaction, the reaction mixture was 
extracted with diethyl ether (10 mL × 10). Then, the extract was washed with sat. aq. 
Na₂SO₃ solution. The organic layer was dried over Na₂SO₄. After removal of the solvent 
under reduced pressure, 2,4-diphenylthiazole was obtained in the crude state. Pure 
2,4-diphenylthiazol (15c) was obtained by flash short column chromatography on silica 
gel (CHCl₃:Hexane = 1:1) in 96 % yield.

Reuse of [Bmim]PF₆: 
After extraction of the reaction mixture with diethyl ether, the ionic liquid was washed
with water (1 mL). The mixture was dried with a vacuum pump for 2 h at 80°C. To a solution of acetophenone (1 mmol) in [Bmim]PF$_6$ (1.5 mL) were added $p$-TsOH·H$_2$O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 12.5 h at room temperature. Then, benzthioamide and K$_2$CO$_3$ (1.1 mmol) were added and the obtained mixture was stirred for 5 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 10). Then, the extract was washed with sat. aq. Na$_2$SO$_3$ solution. The organic layer was dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, 2,4-diphenylthiazole was obtained in the crude state. Pure 2,4-diphenylthiazole was obtained by flash short column chromatography on silica gel (CHCl$_3$; Hexane = 1:1) in 97% yield.

2-Phenyl-4-(4'-methoxyphenyl)thiazole (15a): mp 126°C - 127°C (lit.$^{31}$ mp 134°C - 135°C). IR(Nujol): 3748, 3648, 2309, 1607, 1520, 1307, 1255, 1172, 1029, 979, 833, 737, 722 cm$^{-1}$; $^1$H NMR(500 MHz, CDCl$_3$): $\delta = 8.03$ (d, 2H, $J = 6.3$ Hz, ArH), 7.93 (d, 2H, $J = 8.6$ Hz, ArH), 7.45-7.43 (m, 3H, ArH), 7.34 (s, 1H, thiazole), 6.97 (d, 2H, $J = 9.1$ Hz, ArH), 3.86 (s, 3H, -OCH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 167.6, 159.6, 156.1, 133.8, 129.9, 128.8, 127.7, 127.5, 126.5, 114.0, 110.8, 55.3.

2-Phenyl-4-(4'-methylphenyl)thiazole (15b): mp 108°C (lit.$^{32}$ mp 116°C); IR(Nujol) 3853, 3749, 3648, 2309, 1698, 1540, 1507, 973, 722 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 8.04 - 8.02 (d, 2H, $J = 6.3$ Hz, ArH), 7.89 - 7.87 (d, 2H, $J = 8.0$ Hz, ArH), 7.46 - 7.41 (m, 3H, ArH), 7.40 (s, 1H, thiazole), 7.25 - 7.23 (d, 2H, $J = 6.3$ Hz, ArH), 2.39 (s, 3H, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 167.6, 156.3, 137.9, 133.8, 131.8, 129.9, 129.3, 128.8, 126.5, 111.8, 21.2.

2,4-Diphenylthiazole (15c): mp 78°C (lit.$^{32}$ mp 75°C - 78°C). IR(Nujol) 760, 725, 465 cm$^{-1}$; $^1$H NMR(500 MHz, CDCl$_3$): $\delta =$ 8.05 (d, 2H, $J = 8.0$ Hz, ArH), 8.00 (d, 2H, $J = 8.0$ Hz, ArH), 7.49 - 7.42 (m, 6H, thiazole, ArH), 7.35 (t, 1H, $J = 7.4$ Hz, ArH); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 167.8, 156.2, 134.4, 133.7, 130.0, 128.8, 128.7, 128.1, 126.5, 126.4, 112.5.

2-Phenyl-4-(4'-chlorophenyl)thiazole (15d): mp 128°C (lit.$^{31}$ mp 131°C - 132°C). IR(Nujol) 1235, 1051, 766, 722 cm$^{-1}$; $^1$H NMR(500 MHz, CDCl$_3$): $\delta =$ 8.03 (d, 2H, $J = 8.0$ Hz, ArH), 7.93 (d, 2H, $J = 8.5$ Hz, ArH), 7.48 - 7.44 (m, 4H, ArH, thiazole), 7.41 (d, 2H, $J = 8.5$ Hz, ArH); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 168.1, 155.0, 133.9, 133.5, 132.9, 130.1, 128.9, 128.8, 127.6, 126.5, 112.8.
2-Phenyl-4-(4'-nitrophenyl)thiazole (15e): mp 125°C - 127°C (lit. mp 122°C); IR (Nujol) 1597, 1509, 1341, 1058, 974, 842, 734, 665 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.31 (d, 2H, ArH), 8.17 (d, 2H, ArH), 8.06 · 8.03 (m, 2H, ArH), 7.69 (s, 1H, thiazole), 7.52 · 7.48 (m, 3H, ArH); ¹³C NMR (125 MHz, CDCl₃): δ = 168.7, 153.7, 147.2, 140.2, 133.1, 130.5, 129.0, 126.9, 126.6, 124.1, 115.9.

2,4-Diphenyl-5-methylthiazole (15f): mp 75°C - 76°C (lit. mp 76°C); IR (Nujol) 2723, 1306, 970, 760, 721, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.96 (d, 2H, J = 6.4 Hz, ArH), 7.73 (d, 2H, J = 6.8 Hz, ArH), 7.48 - 7.39 (m, 6H, ArH, thiazole), 2.61 (s, 3H, -CH₃); ¹³C NMR (100 MHz, CDCl₃): δ = 163.5, 151.9, 135.1, 133.8, 129.5, 128.7, 128.6, 128.3, 127.5, 126.2, 12.8.

2-Phenyl-4-(2'-thienyl)thiazole (15h): mp 58 - 60°C (lit. mp 69°C - 71°C); IR (Nujol) 1664, 1024, 970, 763, 691, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 8.04 · 8.01 (m, 2H, ArH), 7.53 (dd, 1H, J = 3.6 Hz, J = 1.1 Hz, thienyl), 7.49 · 7.45 (m, 3H, ArH), 7.35 (s, 1H, thiazole), 7.32 (dd, 1H, J = 5.0 Hz, J = 1.1 Hz, thienyl), 7.10 (dd, 1H, J = 6.4 Hz, J = 5.2 Hz, thienyl); ¹³C NMR (125 MHz, CDCl₃): δ = 167.9, 150.7, 138.3, 133.8, 130.1, 128.9, 127.6, 126.6, 125.3, 124.2, 111.3.

4-Butyl-2-phenyl-5-pentylthiazole (15k): Oil. IR (neat) 2928, 2857, 1536, 1461, 1248, 991, 760, 689 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, 2H, J = 6.6 Hz, ArH), 7.41 - 7.33 (m, 3H, ArH), 2.75 (t, 2H, J = 7.5 Hz, -CH₂-), 2.68 (t, 2H, J = 7.5 Hz, -CH₂-), 1.71 (quant, 2H, J = 7.5 Hz, -CH₂-), 1.63 (quant, 2H, J = 7.8 Hz, -CH₂-), 1.46 · 1.33 (m, 6H, -CH₂-), 0.95 (t, 3H, J = 7.3 Hz, -CH₃), 0.90 (t, 3H, J = 7.1 Hz, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 163.5, 153.4, 134.2, 132.7, 129.2, 128.7, 126.1, 34.2, 31.7, 29.6, 29.2, 26.1, 22.5, 22.2, 14.0, 13.8; HRMS Calcd for C₁₈H₂₆NS 288.1780, Found: 288.1774.

4-Phenyl-2-(4'-methoxyphenyl)thiazole (15l): mp 96°C - 98°C (lit. mp 101°C); IR(Nujol) 1519, 972, 833, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, 2H, J = 7.3 Hz, ArH), 7.93 (d, 2H, J = 8.2 Hz, ArH), 7.46 · 7.42 (m, 2H, ArH, thiazole), 7.34 (t, 1H, J = 7.3 Hz, ArH) 7.26 (d, 1H, J = 6.4 Hz, ArH) 2.41 (s, 3H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 168.0, 156.1, 140.2, 134.6, 131.1, 129.5, 128.6, 128.0, 126.5, 126.4, 112.1, 21.4.

4-Phenyl-2-(4'-methoxyphenyl)thiazole (15m): mp 96°C - 98°C (lit. mp 101°C); IR(Nujol) 1519, 1254, 979, 833, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (d, 2H, J = 7.3 Hz, ArH), 7.93 (d, 2H, J = 8.2 Hz, ArH), 7.46 · 7.42 (m, 2H, ArH, thiazole), 7.34 (t, 1H, J = 7.3 Hz, ArH) 7.26 (d, 1H, J = 6.4 Hz, ArH) 2.41 (s, 3H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 168.0, 156.1, 140.2, 134.6, 131.1, 129.5, 128.6, 128.0, 126.5, 126.4, 112.1, 21.4.
9.1 Hz, ArH), 7.44 (t, 2H, J = 7.3 Hz, ArH), 7.41 (s, 1H, thiazole), 7.34 (t, 1H, J = 7.3 Hz, ArH), 3.86 (s, 3H, OCH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 167.6, 161.1, 155.9, 134.6, 128.6, 128.0, 126.7, 126.3, 114.2, 111.7, 55.3.

2-(4'-Nitrophenyl)-4-Phenylthiazol (15n): mp 162°C - 164°C (lit. mp 164°C - 165°C); IR(Nujol) 1595, 1512, 1340, 848, 751, 722, 687 cm⁻¹; ¹H NMR(500 MHz, CDCl₃): δ = 8.33 (d, 2H, J = 9.2 Hz, ArH), 8.22 (d, 2H, J = 9.2 Hz, ArH), 8.00 (d, 2H, J = 6.8 Hz, ArH), 7.62 (s, 1H, thiazol), 7.47 (t, 1H, J = 7.4 Hz, ArH), 7.39 (t, 1H, J = 7.4 Hz, ArH); ¹³C NMR (100 MHz, CDCl₃): δ = 164.7, 157.3, 148.4, 139.1, 133.8, 128.8, 128.6, 127.1, 126.4, 124.3, 114.5.

2-Methyl-4-phenylthiazole (15o): mp 64°C (lit. mp 64°C); IR(Nujol) 740, 726, 692, 675 cm⁻¹; ¹H NMR(400 MHz, CDCl₃): δ = 7.87 (d, 2H, J = 6.8 Hz, ArH), 7.41 (t, 2H, J = 7.8 Hz, ArH), 7.33-7.30 (m, 2H, ArH, thiazole), 2.78 (s, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃): δ = 165.7, 155.1, 134.5, 128.6, 127.9, 126.2, 112.2, 19.3.
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List of Publications

Papers


Poster
1) α-Bromination of Ketones Using NBS in Ionic Liquids and its application of preparation of Thiazoles.
The 90th Annual Meeting of Japan Chemical Society, Osaka, March 26, 2010.

2) Intramolecular Amidehydroxylation of N-Alkenyl sulfonamides with Inorganic Reagent.
The 92th Annual Meeting of Japan Chemical Society, Tokyo, March 27, 2012.

3) Intramolecular Bromo-oxygenation of Alkenylicarboxylic acids and Alkenylalcohols via Oxidative Umpolung of Alkali Metal Bromides.
The 93th Annual Meeting of Japan Chemical Society, Shiga, March 24, 2013.

4) Intramolecular Aminohydroxylation of N-Alkenyl Sulphonamides with Inorganic Reagent.
IKCOC-12, Kyoto, PC-063, November 15, 2012.

Oral
1) Intramolecular Bromoamidation of N-Alkenylsulfonamides via Oxidative Umpolung Reaction of Inorganic Bromides.
The 91th Annual Meeting of Japan Chemical Society, Kanagawa, March 29, 2011
2) Intramolecular Bromo-etherification *via* the Oxidative Umpolung of Bromide Ion. The 94th Annual Meeting of Japan Chemical Society, Kanagawa, March 29, 2014